

Comments by Michael Honeycutt, Ph.D., with the Texas Commission on Environmental Quality Regarding the Use of Science in, and Implications of, EPA's Chemical Risk Assessments

On behalf of the Texas Commission on Environmental Quality (TCEQ), I would like to touch briefly on Texas' perspective on the science that EPA is using, or not using, for chemical risk assessments in recent years and the implications for regulatory agencies and the public.

In years past, we have had disagreements with EPA, but they have not been on science issues so much as on science policy issues. An example would be that EPA does not want to consider TCEQ rules, which are more stringent in many cases, when addressing a cleanup site in Texas. However, we have always been able to work out our differences amicably.

But in recent years, EPA chemical risk assessments have become more precautionary in nature *in lieu* of relying on scientific data. The heart of the matter is that EPA is moving toward the philosophy that there is no safe level of exposure to a chemical, which is contrary to the cornerstone of the science of toxicology. This change in philosophy results in unrealistically low levels that they consider safe. As a result, naturally occurring levels of chemicals will be higher than EPA's safe level.

For example, using EPA's most recent assessment of formaldehyde, the formaldehyde in your breath that results from normal body functions would be over 5 times higher than the highest level that EPA would call safe. Formaldehyde is naturally formed in the air from the breakdown of chemicals released from vegetation. According to available air data, the only places that would have safe air would be remote locations such as the arctic or South Pacific islands. Using EPA's most recent assessment of arsenic and available data from recent fish studies, all fish and shellfish would contain levels that are higher than the highest levels EPA would consider safe. You may have heard of the recent Dr. Oz controversy about arsenic in apple juice where he mistakenly assumed all types of arsenic in the juice were the most toxic form. We accounted for the most toxic form of arsenic in fish and shellfish in looking at the food safety implications of EPA's new draft arsenic assessment. Fish is not the only issue, normal dietary food and drinking water consumption would also be substantially higher than EPA's safe level. We know this is not true. We are not seeing the health effects that would be expected in the general population because these values are not based on good science.

While we agree with EPA on being cautious in areas where we do not have good science, we strongly believe that good science should not be ignored and should trump EPA's overuse of precaution. Formaldehyde is again a good example of this. EPA's recent conclusion that formaldehyde causes leukemia in humans is based on one study that did not show effects at occupational levels, much less

environmental levels. However, a wealth of solid scientific data show that formaldehyde cannot cause cancer outside of the respiratory tract, but EPA dismissed these data.

TCEQ is not the only organization concerned about the science behind EPA's recent risk assessments. The National Academy of Sciences, many prominent academic researchers, other states, and other countries have noted the lack of good science in these assessments. For that reason, states like Texas are conducting more of their own chemical risk assessments.

Because of the lack of scientific defensibility and the implications of EPA's new chemical assessments, we decided to develop our own chemical assessments. We have written two state-of-the-science based guidance documents, had them externally scientific peer reviewed by panels of eminent scientists including scientists with EPA, California EPA, and Canada, and are in the process of putting our latest document through another round of public comment.

We had no desire to use our limited resources to develop chemical risk assessments that we have historically been able to rely on EPA for. However, the implications of EPA's newer assessments have forced our hand. EPA's new assessments will unnecessarily scare the public and may actually harm public health by diverting public, industry, and government attention and resources away from public health issues that may pose more of a risk. For example, EPA currently encourages pregnant women to limit their consumption of fish due to concerns from mercury. However, numerous recent studies show that the health benefit from pregnant women eating fish outweighs potential risks from mercury. If EPA finalizes their draft arsenic value as it currently stands, then the public, the media, and advocacy groups would perceive fish as unsafe, resulting in even more pregnant women avoiding fish and its proven health benefits for them and their infants.

There are also significant implications for remediation programs all across the country. Typical soil and water concentrations of chemicals, some even naturally occurring, would be considered unsafe. In other words, there is no safe place to live. How can you clean to below background levels if background levels are unsafe? All replacement soils that we would use to fill in a backyard would also contain these unsafe background levels. Where are we going to put all of this so-called contaminated soil? Your constituents will not stand for having soil and water that is deemed unsafe by EPA's new risk assessments; even if it is naturally occurring and we cannot do anything about it.

These are just some of the issues that you and I will have to address if EPA stays on their course of not using good science. Attached are the technical comments (excluding appendices) that TCEQ has submitted to EPA recently which outline in more detail the numerous scientific shortcomings of recent EPA chemical risk assessments.

**Supplemental Information for Comments by Michael Honeycutt, Ph.D.,
with the Texas Commission on Environmental Quality Regarding the Use
of Science in, and Implications of, EPA's Chemical Risk Assessments**

Attachment A – TCEQ Comments on EPA Formaldehyde Assessment

**Texas Commission on Environmental Quality
Comments Regarding the U.S. Environmental Protection Agency
Draft Toxicological Review of Formaldehyde in Support of
Summary Information on the Integrated Risk Information System (IRIS)
Notice of Public Comment Period and Listening Session
75 FR 30825, June 2, 2010
Docket ID No. EPA-HQ-ORD-2010-0396**

On June 2, 2010, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register/Vol. 75, No. 105/Wednesday, June 2, 2010/Notices) of a 90-day public comment period (ending August 31, 2010) for the, “Draft Toxicological Review of Formaldehyde in Support of Summary Information on the Integrated Risk Information System (IRIS),” hereafter referred to as the draft IRIS review (EPA/635/R-10/002A). The draft IRIS review provides draft inhalation unit risk factors (URFs) for nasopharyngeal cancer, leukemia, Hodgkin lymphoma, and a combined URF for formaldehyde. It also provides a draft inhalation reference concentration (RfC), although EPA has not historically calculated an RfC for formaldehyde. The Texas Commission on Environmental Quality (TCEQ) has developed comments on the draft IRIS review to the extent practicable in the time allotted by EPA, focusing on the draft URFs, and provides the following limited comments for EPA consideration.

General Comment:

The assessment of the carcinogenic (and non-carcinogenic) potential of formaldehyde has great implications both in a regulatory context and in the public’s perception of risk. Given their important role in the protection of public health, EPA regulatory risk assessors have a duty to perform the most scientifically-defensible assessments possible while giving careful and due consideration to comments and recommendations from other regulatory agencies, the public, external experts, stakeholders, etc. Although regulatory risk assessors have a penchant for erring on the side of health-protectiveness and conservative defaults, if erring on the side of conservatism significantly overestimates risk or hazard and is not fully justified, then harm to public health may result from diverting public, industry, and government attention and resources away from chemicals which may represent more of a public health risk at environmental levels. Therefore, TCEQ encourages EPA to give full, thoughtful, and careful consideration and evaluation to comments and recommendations from TCEQ, other regulatory agencies, the public, and external experts.

90-Day Comment Period:

The 90-day comment period is insufficient for regulatory agencies and others to provide thorough and meaningful comments based on an in-depth review and analysis of the draft IRIS review. There is great complexity associated with multiple issues relevant to the assessment of formaldehyde inhalation risk and hazard. The draft IRIS review alone is 1,043 pages, and there are hundreds of pages (at a bare minimum) of other documents and studies relevant to the assessment of formaldehyde risk and hazard due to inhalation exposure. Given the complexity and volume of relevant materials, it is impracticable for EPA to expect detailed specific comments from external experts given the short period allowed for a critical review of the draft IRIS review and procedures employed by EPA. The 90-day comment period only allows a very cursory review of the draft IRIS review at best, leads to a less-than-desirable level of

transparency and peer review, and undermines confidence in the process. Consequently, TCEQ is only able to provide preliminary comments based on a cursory review. If EPA seeks detailed and meaningful public input and technical comments, at a minimum EPA should extend the comment period at least 90 days past the August 31 deadline to allow stakeholders to perform a more detailed review of the volumes of relevant information and to comment on problematic issues associated with the draft IRIS review.

Toxicology-Based Comments:

Key Study for Hodgkin Lymphoma and Leukemia Unit Risk Factors

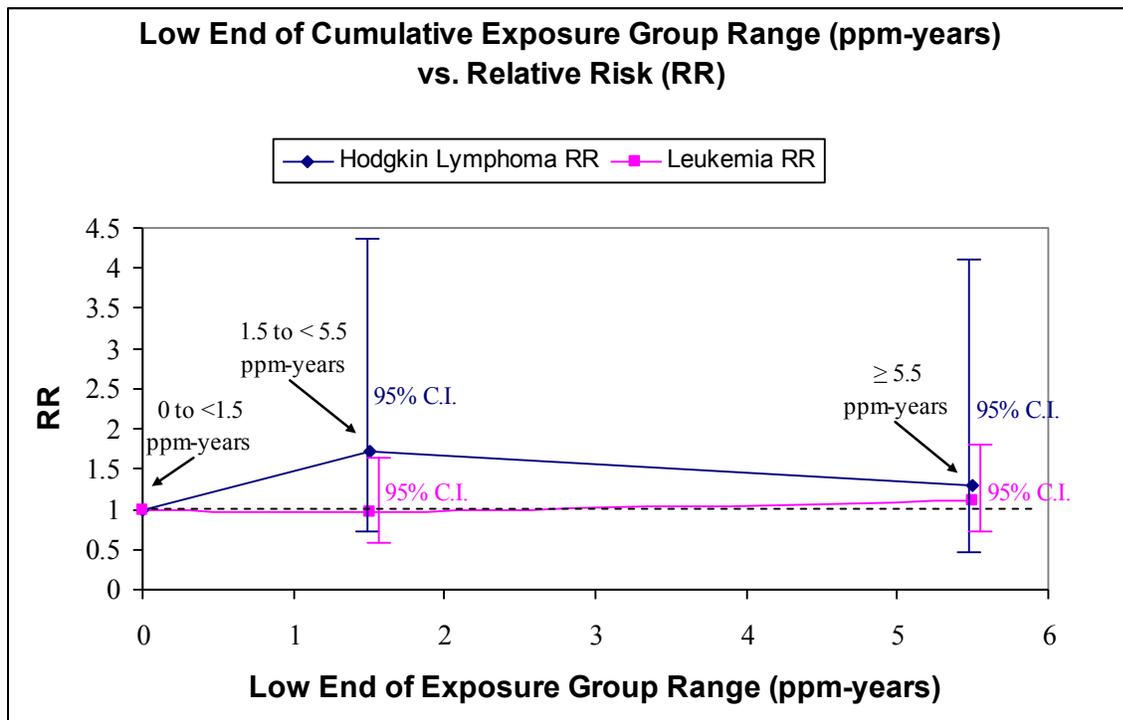
EPA utilizes the Beane Freeman et al. (2009) study to calculate draft URFs for Hodgkin lymphoma and leukemia. While there were statistically significant trends for Hodgkin lymphoma and leukemia with peak exposure, there were no statistically significant trends for any lymphohematopoietic malignancy with cumulative exposure. EPA indicates (p. 5-91) that it is not clear how to extrapolate risk estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures, and that the average exposure metric is also problematic because it suggests that duration of exposure is not important. Because EPA could not derive URFs for Hodgkin lymphoma and leukemia based on the dose metric for which there was a significant association (peak exposure), EPA used a dose metric for which there was no significant association (cumulative exposure) despite the fact that dose-response data for this dose metric are inadequate. EPA calculated draft URFs based on cumulative exposure despite that: (1) there were no statistically significant trends for Hodgkin lymphoma and leukemia with cumulative exposure; (2) regardless of statistical significance considerations, there is no apparent dose-response relationship between cumulative exposure and risk to provide adequate data for URF development; (3) if there is a causal relationship, study results indicate that peak exposure (as opposed to cumulative) is the most significant determinant of risk; and (4) if there is a causal relationship, study results suggest that duration of exposure, which is inherently part of the cumulative exposure dose metric, is not important (per EPA, p. 5-91).

Dose-Response Data

A primary reason that EPA used the cumulative exposure metric in order to be able to derive URFs is that, “the elevations in risk with that metric were consistent with significant elevations observed with the peak exposure (for Hodgkin lymphoma and leukemia).” However, this is not the case. While the relative risks (RR) for Hodgkin lymphoma and leukemia may show a monotonic dose-response relationship with peak exposure, the RRs do not appear to show a dose-response relationship for the cumulative exposure dose metric used by EPA. For example, for Hodgkin lymphoma the RR for the highest cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71). For leukemia, the RRs for the highest and medium cumulative dose groups are essentially equal to 1 (RRs of 1.11 and 0.96, respectively), consistent with no elevated risk. The RRs for Hodgkin lymphoma and leukemia based on cumulative exposure (RRs of 0.96-1.71) are not consistent with a strong relationship and all RR confidence intervals easily include 1 (i.e., the lower end of the RR confidence intervals range from 0.40 to 0.70), consistent with the possibility of no elevated risk. Additionally, the Beane Freeman et al. (2009) study is not informative regarding what the RR might be for environmental exposures, which would fall into the cumulative exposure category used as the referent group (0-1.5 ppm-years), and the intermittent peak exposures associated with elevated RRs for workers (> 2 ppm) are significantly higher than environmentally-relevant levels. EPA does not attempt to provide a robust

justification for use of the cumulative exposure metric, and given the results of the Beane Freeman et al. (2009) study, TCEQ does not believe a robust justification is possible (i.e., use of the cumulative exposure metric is not scientifically defensible).

In addition, the cancer guidelines (EPA 2005a) recommend use of enough dose groups to provide an indication of the shape of the dose-response curve, as characterization of the shape of the dose-response curve is important in providing relevant dose-response data for assessing human risk. A relatively broad exposure range should make it relatively easy to discern the shape of any underlying dose-response curve in a well-conducted study. However, it is clear based on examination of the figure below that the data from Beane Freeman et al. (2009) provide too few dose groups and do not provide a monotonic dose-response curve, much less provide an indication of any reasonable shape of any underlying dose-response curve. As an example, for Hodgkin lymphoma the RR for the highest cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71). These data are nonsensical from a dose-response perspective and clearly inadequate for derivation of a URF. For leukemia, again, the RRs for the highest and medium cumulative dose groups are essentially equal to 1 (RRs of 1.11 and 0.96, respectively) and do not provide an indication of a dose-response shape or increased risk relevant to environmental exposure for that matter. The ability to fit a line through data points does not necessarily mean that the underlying data adequately define the shape of the dose-response curve, including the critical low dose region. Based on the above considerations, the underlying data modeled by EPA clearly do not provide a basis for dose-response assessment. Dose-response is the cornerstone of toxicology, but the data modeled by EPA do not provide a solid foundation upon which to build these URFs.



In summary, EPA decided to use the cumulative exposure dose metric to calculate draft URFs despite the lack of statistically significant trends, despite not having the necessary dose-response data to do so in a scientifically-defensible manner, despite information suggesting that peak exposure (as opposed to

cumulative) is the most significant determinant of any risk, and despite information suggesting that duration of exposure (inherently part of the cumulative exposure dose metric) is not important (per EPA). To restate EPA's sentence (p. 5-91) in a slightly different but equally valid manner, it is not clear how to extrapolate risk apparently associated with peak exposures to *meaningful* estimates of lifetime extra risk of cancer due to cumulative or average environmental exposure. As data indicate that risk (if any) is most closely related to peak exposure, not cumulative or average exposure, the scientific validity and predictive value of risk estimates (e.g., URFs) calculated based on a cumulative exposure dose metric for which there is no apparent dose-response relationship is highly questionable. These significant issues are in addition to arguments concerning the lack of biological plausibility.

Leukemia and Hodgkin Lymphoma Contribution to the Combined URF

Leukemia URF

The URF for leukemia is by far the highest of the three combined by EPA (nasopharyngeal, Hodgkin lymphoma, leukemia) for the draft URF, contributing 60% of the risk for the combined draft URF. However, the draft URF for leukemia is likely the least scientifically defensible. As indicated above, for leukemia the RRs for the highest and medium cumulative exposure dose groups are essentially equal to 1, with RRs of 1.11 and 0.96, respectively. Obviously, the RR confidence intervals for the highest (0.70-1.74) and medium (0.60-1.56) cumulative exposure dose groups include 1. These RRs and confidence intervals for cumulative exposure are consistent with no elevated risk and there is no significant dose-response for leukemia with cumulative exposure, yet leukemia is the combined URF risk driver. Additionally, there is no dose-response based on average concentration; the RRs for the medium (RR of 1.13) and high (RR of 1.10) exposure groups show no dose-response and are essentially equal to 1 with confidence intervals containing 1 (i.e., the lower end of the RR confidence intervals range from 0.68 to 0.71). Even for peak exposure for which there was a trend, only the highest exposure group (≥ 4 ppm) has a RR greater than 1 (RR of 1.42), and the confidence interval for that group includes 1 (0.92-2.18). The RR for the medium peak exposure group, comprised of workers exposed to much higher than environmentally-relevant concentrations (2 to < 4 ppm), was 0.98 and consistent with no elevated risk.

In summary, the draft combined URF is driven by the URF for leukemia, for which the only RR greater than 1 in the derivation is the RR of 1.11 for the highest cumulative exposure group (≥ 4 ppm). This RR and the associated confidence interval containing 1 (0.70-1.74) are consistent with no excess risk yet will likely drive unachievable outdoor and indoor regulatory air levels (see relevant comment sections below). The URF for leukemia based on cumulative exposure is not scientifically defensible based on RRs essentially equal to 1 and the lack of a statistically significant or apparent dose-response (there are also biological plausibility issues). Based on Beane Freeman et al. (2009) study results, if any association exists between formaldehyde exposure and leukemia it may be with intermittent peak exposures levels greater than 4 ppm, an exposure scenario for which EPA acknowledges (p. 5-91) that no meaningful URF applicable to environmental concentrations can be calculated.

Hodgkin Lymphoma URF

The URF based on Hodgkin lymphoma contributes 23% of the risk for the combined draft URF. Several of the reasons why the URF for leukemia based on cumulative exposure is not scientifically defensible also apply to the URF for Hodgkin lymphoma. There is a lack of a statistically significant trend and lack

of a monotonic dose-response relationship between Hodgkin lymphoma and cumulative exposure. The RR for the highest cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71) and neither indicates a strong relationship. The RR confidence intervals include 1 (i.e., the lower end of the RR confidence intervals range from 0.40 to 0.66) consistent with the possibility of no excess risk, yet this URF will be a significant driver in likely unachievable outdoor and indoor regulatory air levels (see relevant comment sections below). In addition to no significant or apparent dose-response relationship with cumulative exposure, there is none between Hodgkin lymphoma and average exposure. If any association exists between formaldehyde exposure and Hodgkin lymphoma, it may be with intermittent peak exposures levels, an exposure scenario for which EPA acknowledges (p. 5-91) that no meaningful URF applicable to environmental concentrations can be calculated.

Conclusions Regarding the Leukemia and Hodgkin Lymphoma URFs

In summary, the draft URFs for leukemia and Hodgkin lymphoma based on cumulative exposure are not scientifically defensible (e.g., lack of dose-response). If a relationship does exist, it appears to be with peak exposure, and EPA indicates that it is not clear how to extrapolate risk estimates based on the peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures. However, in effect this is exactly what EPA did, extrapolating apparently peak-associated risk to lifetime extra cancer risk by using a dose metric (cumulative exposure) for which there is no dose-response, resulting in URFs of highly questionable meaning. Clearly, EPA should redact these draft URFs. Alternatively, EPA should provide a robust justification for the need to derive URFs for leukemia and Hodgkin lymphoma in the absence of a dose-response for cumulative exposure and scientific defensibility.

Formaldehyde Exposure, Leukemia, and Lymphohematopoietic Cancers

Findings regarding associations between formaldehyde and leukemia are inconsistent across studies, and whether formaldehyde is capable of causing lymphohematopoietic malignancies is not scientifically established and is of great scientific debate and controversy. TCEQ disagrees with EPA (p. 4-535) that human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure, leukemia, and lymphohematopoietic cancers as a group considering the inconsistency of the associations, the weakness of the associations as demonstrated by the RRs and confidence intervals discussed above for the principal study used by EPA, and biological implausibility considerations. As additional examples, for the cohorts summarized by EPA (pp. 4-493 to 4-495), no standardized mortality ratios (SMRs) for lymphohematopoietic cancers are greater than 3, with only 1 of 18 greater than 2, indicating a very weak association if any. In fact, 5 of 18 SMRs are less than 1 and 67% of the SMR confidence intervals include 1, consistent with a lack of association. For leukemia, only 3 of the 21 SMRs exceed 2, with 5 being less than 1, overall consistent with a lack of association. Additionally, in 100% of the cases where leukemia SMR confidence intervals are given they include 1. EPA should weigh the human epidemiological evidence more carefully before deciding to calculate URFs based on the Beane Freeman et al. (2009) study where the association was with peak exposure and not the cumulative exposure dose metric used by EPA (a separate issue).

Implications of Lu et al. (2010) for EPA URF Development

A well-conducted study by Lu et al. (2010) has very recently been able to clearly differentiate between endogenous and exogenous formaldehyde-induced DNA adducts and DNA-DNA cross-links, allowing the quantitative examination of formaldehyde-induced adducts and cross-links in a multitude of tissues following inhalation exposure. This study shows that even in rats exposed to much higher concentrations (10,000 ppb) than environmental exposures of humans, exogenous formaldehyde-induced adducts and cross-links only occur in the rat nasal mucosa (the clear target site of rat carcinogenesis) and not at sites remote to the portal of entry. In other words, this study clearly shows that exogenous formaldehyde-induced genotoxic effects at sites remote to the portal of entry are implausible. Additionally and directly relevant to the hypothesis by EPA and others that hematopoietic stem cells/early progenitor cells in the circulation or residing in the nasal passages may be exposed in the nose and travel to the bone marrow to be transformed into leukemia cells (e.g., pp. 4-529 to 4-535), Lu et al. (2010) used a very sensitive method (the method could detect levels \approx 30 times less than the number of adducts from endogenous formaldehyde) to show that neither white blood cells nor bone marrow contained exogenous formaldehyde-induced DNA adducts (or cross-links). The EPA draft IRIS review gives no serious evaluation of the significant implications of these study results for the scientific defensibility of deriving URFs for Hodgkin lymphoma and leukemia. The significant implications of this recent research are inconsistent with deriving URFs for Hodgkin lymphoma and leukemia and were simply ignored in the draft IRIS review document.

Regression Coefficient for Nasopharyngeal Cancer

EPA utilizes a regression coefficient (β) based on nasopharyngeal cancer *mortality* to calculate the URF for nasopharyngeal cancer *incidence* (pp. 5-83 to 5-84). However, the survival rate for nasopharyngeal cancer is significant (\approx 50%), and no robust justification is provided for the assumption or expectation that nasopharyngeal cancer mortality and incidence share the same dose-response relationship and therefore use of a β based on mortality is justified for incidence.

Application of Age-Dependent Adjustment Factors

EPA indicates that: (1) there is an adequate weight of evidence to consider formaldehyde-induced mutations relevant to human carcinogenic risk (p. 6-24); (2) that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic mode of action (MOA) (p. 6-25); and (3) therefore, age-dependent adjustment factors (ADAFs) should be applied in accordance with EPA guidance (EPA 2005b) (p. 5-104). However, EPA provides no discussion concerning the scientific defensibility of applying ADAFs derived from data for mutagenic carcinogens to a chemical like formaldehyde with a mixed MOA for which EPA has only determined that mutagenicity plays a part.

Implementation-Based Comments:

Implications of the URF for Ambient and Indoor Air

TCEQ notes that the 1 in 100,000 excess risk air concentration of 0.08 ppb based on the draft URF is not met anywhere in the world, indoors or outdoors (or in our own breath). This includes remote locations such as Alert, Nunavut, Canada, located in the arctic only 500 miles from the north pole (average of 0.4 ppb), and the remote South Pacific island of Eniwetok Atoll (average of 0.4 ppb) (IARC 2006). The

average reported for Alert, Nunavut is based on data collected during polar night, a time during which contributions from photochemical oxidation of hydrocarbons would be negligible.

TCEQ risk-based air monitoring comparison values are set at an excess risk level of 1 in 100,000. Using the draft URF and a 1 in 100,000 air concentration (0.08 ppb) would mean that formaldehyde levels at the arctic's Alert, Nunavut and the South Pacific's remote Eniwetok Atoll island would need to be reduced by a factor of at least 5 times. Even the 1 in 10,000 excess risk air concentration of 0.8 ppb based on the draft URF is almost not met anywhere in the world, with a few exceptions such as remote locations like Alert, Nunavut and Eniwetok Atoll (averages of 0.4 ppb) (IARC 2006). As levels of formaldehyde in indoor air are often significantly higher than levels outdoors, indoor air concentrations would be expected to significantly exceed (i.e., at least by an order of magnitude) even the 1 in 10,000 excess risk air concentration (IARC 2006). Use of the draft URF would imply that air neither indoors nor outdoors (or even your own breath, see below) is safe from a regulatory perspective.

Implications of the URF for Endogenously-Produced Formaldehyde

Formaldehyde is produced endogenously in the human body. TCEQ notes that the air concentration corresponding to the upper end of the EPA acceptable risk range (1 in 10,000 excess cancer risk) using the draft URF is 0.8 ppb (p. 5-143). However, even this highest regulatory-acceptable air concentration is over 5 times lower than the median normal human breath level (4.3 ppb) reported in 344 healthy men and women (positive alveolar gradient, negligible room air concentrations reported in Moser et al. 2005), and is 50 times lower than the reported 97.5th percentile normal formaldehyde breath level (40 ppb). At face value, use of this draft URF and data imply that formaldehyde breath levels resulting from normal endogenous production would clearly represent an unacceptable level of risk from a regulatory perspective (e.g., risk of 5.4E-04 to 5.0E-03 using EPA's draft URF and the median and 97.5th percentile normal breath levels). Using the lower end of the acceptable risk level (1 in 1,000,000), the corresponding air concentration is 0.008 ppb, which is 537 times lower than the median reported breath level and 5,000 times lower than the 97.5th percentile normal formaldehyde breath level (positive alveolar gradient, negligible room air concentrations reported in Moser et al. 2005). Regulating formaldehyde at concentrations anywhere from 5-5,000 times lower than normal breath concentrations presumably resulting from normal endogenous production simply makes no sense as it offers insignificant risk reduction compared to the risk which would result from normal breath levels due to endogenous production (assuming there is in fact risk at these levels).

References

Beane-Freeman, LE; Blair, A; Lubin, JH; et al. (2009) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. *J Natl Cancer Inst* 101:751–761.

International Agency for Research on Cancer (IARC). 2006. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Vol. 88: Formaldehyde, 2-butoxyethanol, and 1-tert-butoxypropan-2-ol. World Health Organization, Lyon, France.

Moser B, Bodrogi F, Eibl G, et al. 2005. Mass spectrometric profile of exhaled breath-field study by PTR-MS. *Respir Physiol Neurobiol* 145:295-300.

U.S. Environmental Protection Agency (EPA). 2005a. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC: EPA/630/P-03/001B.

U.S. Environmental Protection Agency (EPA). 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Washington, DC: EPA/630/R-03/003F.

Attachment B – TCEQ Comments on EPA Arsenic Assessment

Texas Commission on Environmental Quality
Comments Regarding the United States Environmental Protection Agency
Draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the
Integrated Risk Information System (IRIS)
Notice of Public Comment Period
75 FR 7477, February 19, 2010
Docket ID No. EPA–HQ–ORD–2010–0123

The Texas Commission on Environmental Quality (TCEQ) provides the following comments on the United States Environmental Protection Agency (USEPA) announcement of the public comment period regarding its *Draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)*.

On February 19, 2010, the USEPA published a Federal Register notice of a 60-day public comment period (ending April 20, 2010) for the *Draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)* (Federal Register/Vol. 75, No. 33/Friday, February 19, 2010/Notices). USEPA will only guarantee that comments submitted by March 26, 2010, will be provided to the Scientific Advisory Board in time for their meeting to consider the final draft EPA document. This final draft USEPA document (EPA/635/R-10/001) derives an oral slope factor (SFo) for arsenic to ultimately be published on IRIS. To the extent practicable in the time allotted by USEPA, Toxicology Division staff of the TCEQ have developed comments for USEPA consideration.

60-Day Public Comment Period

The 60-day comment period is insufficient for regulatory agencies and others to provide meaningful comments based on an in-depth review and analysis of the derivation of the final draft SFo. There is great complexity associated with multiple issues relevant to the assessment of arsenic risk due to oral exposure. The final draft document alone is 575 pages, with the Science Advisory Board (SAB) comments on three USEPA documents relevant to USEPA's final draft arsenic assessment being almost another 100 pages, and hundreds of pages (at a bare minimum) of other documents (e.g., National Research Council 1991 and 2001 reviews) and studies relevant to the assessment of risk due to oral arsenic exposure. Given the complexity and volume of relevant materials, it is impracticable for USEPA to expect detailed specific comments from external experts given the short period allowed for a critical review of the document and procedures employed by USEPA. To exacerbate the short review time problem, the 5-day Society of Toxicology 49th Annual Meeting (March 7-11) and the 3-day Alliance for Risk Assessment dose-response conference (*Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment*, March 16-18) fall within the review period, and TCEQ staff and many other external expert peer reviewers will be in attendance. The 60-day comment period only allows a cursory review of the document at best, leads to a less-than-desirable level of peer review and transparency, and undermines confidence in the final draft SFo value. Consequently, TCEQ is only able to provide preliminary comments on the final draft SFo value, barely scratching the surface of the document. The comment deadline should be extended at least 60 days past the current April 20th deadline to allow for a detailed review of the hundreds of pages of documents (at a bare minimum) and complex issues relevant to derivation of the final draft SFo for arsenic.

Arsenic SFo

The final draft SFo of 25.7 per mg/kg-day represents a 17-fold increase over the SFo currently on IRIS (1.5 per mg/kg-day). This is a significant change in the estimated carcinogenic potency of arsenic. Arsenic already has a relatively high SFo and such a large change would have far reaching regulatory implications. Thus, the final draft SFo deserves greater scrutiny than allowed by the 60-day public comment period. In addition to TCEQ's concerns, we understand both external groups and internal USEPA staff have expressed serious concerns about the final draft SFo. Brief discussions of four areas of TCEQ concern relevant to the toxicological basis for the derivation of the final draft SFo are provided below. This discussion is followed by comments on some practical implications that highlight the importance of EPA developing a scientifically-defensible SFo for arsenic.

Toxicological Concerns with the Final Draft Arsenic SFo

Water Intake and Non-water Arsenic Intake

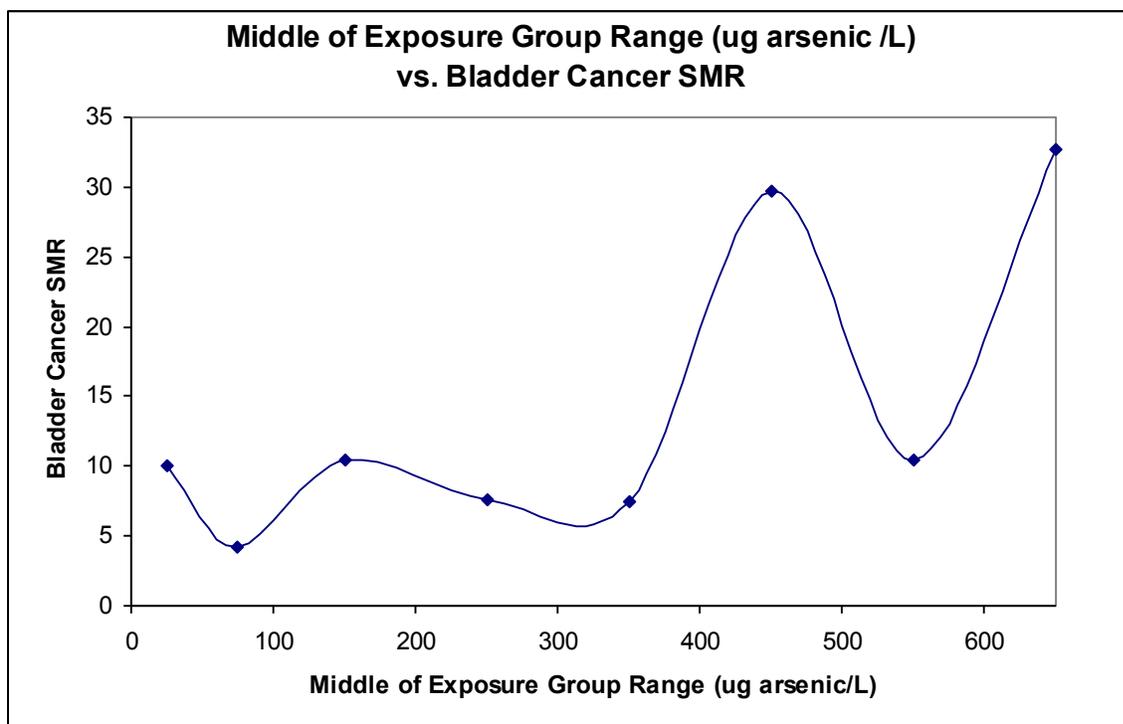
The final draft USEPA document acknowledges that there is significant uncertainty associated with water intake (e.g., see page 117 “few precise data,” “limited information”; page 120 “drinking water exposure information is not available for individual study subjects”) and non-water arsenic intake (e.g., see page 118 “relatively little data,” “considerable confusion about” how to include this; page 123 “data supporting this value are scarce”) for the exposed Taiwanese populations. Data on variations in arsenic drinking water levels with time are also lacking. TCEQ believes it unreasonable to exclude arsenic intake from water used for cooking rice and produce (e.g., rice and yams are staples) from dietary intake for exposed populations for the primary analysis as indirect water intake estimates are around 1 L/day (page 124), significantly underestimating dose. Additionally, there are no drinking water arsenic data for the reference populations, and TCEQ has serious concerns about the reasonableness of assuming zero arsenic drinking water intake for reference populations. TCEQ also has significant concerns about assuming the same non-water arsenic intake (10 µg/day) for both the reference and exposed populations given that USEPA acknowledges that exposed populations may be exposed to 15-211 µg/day (50 µg/day average) from food (page 123). The examination of such issues in a sensitivity analysis does not alleviate USEPA's duty to derive the most accurate SFo possible in the primary analysis by incorporation of the most informed estimates possible for factors known to be critical for derivation of a reasonably predictive SFo (e.g., population-specific factors influencing total dose such as indirect water and food intake).

USEPA appears to lack data sufficient to establish the extent to which total arsenic exposure (i.e., dose) differed for the exposed and “nonexposed” populations, making derivation of a reasonably accurate SFo problematic. Accurate water intake and non-water arsenic intake data are critical in deriving defensible dose estimates and a scientifically-defensible carcinogenic assessment, but are lacking. The admitted absence of accurate dose estimates due to lack of good water intake and non-water arsenic intake data precludes the conduction/derivation of an accurate dose-response assessment and SFo.

Dose-Response Data

USEPA used lung and bladder mortality data from Morales et al. (2000) for the dose-response assessment for the final draft SFo. Morales et al. (2000) uses these mortality data to calculate standardized mortality ratios (SMRs) and notes, “Although the computed SMRs display a large amount of noise, there appear to

be higher SMRs at high exposure levels compared to exposures in the lower range, especially for bladder and lung cancer.” To say that there is “noise” in the SMRs over the eight exposure categories is an understatement. Dose-response is the cornerstone of toxicology, but the lung and bladder mortality data (SMRs) from Morales et al. (2000) provide a poor basis for dose-response assessment as a dose-response is not apparent and not monotonic. Breaking the data down into the form of age-specific person-years at risk and cancer deaths does not improve the basis for dose-response assessment; it only obscures the lack of a good dose-response which is readily apparent from examination of the SMRs. For example, for lung cancer, SMRs greater than 3 were essentially only obtained for drinking water levels greater than 400 µg/L, which does not indicate a particularly strong dose-response. Even at 500-600 µg/L, the SMR was only 3.32. For bladder cancer, the dose-response data from Morales et al. (2000) and used by USEPA do a poor job of characterizing the shape of the dose-response curve, as can be seen from the figure below (line added for emphasis).



The cancer guidelines (USEPA 2005) recommend use of enough dose groups to provide an indication of the shape of the dose-response curve, as characterization of the shape of the dose-response curve is important in providing relevant dose-response data for assessing human risk. A relatively large exposure range should make it relatively easy to discern the shape of any underlying dose-response curve in a well-conducted study. However, despite the eight exposure groups in Morales et al. (2000), the figure above illustrates that the shape of the dose-response curve for bladder cancer, which had the highest SMRs by far, has not been adequately defined by the dose-response data selected by USEPA for derivation of the SFO. As an example, the SMR for the 0-50 µg/L exposure group (plotted at 25 µg/L) is higher than that for the 300-400 µg/L exposure group (plotted at 350 µg/L), and similar to that for the 500-600 µg/L exposure group (plotted at 550 µg/L). The ability to fit a line through data points does not necessarily mean that the underlying data adequately define the shape of the dose-response curve, including the

critical low dose region. Based on the above considerations, the underlying data modeled by USEPA provide a poor basis for dose-response assessment.

Biological Effects of Ionizing Radiations (BEIR) IV Model

Appendix E to the final draft USEPA document indicates that a modified BEIR IV model was used, which takes as inputs the dose-response “b” coefficient, background cancer incidence data, and age-specific mortality data, to estimate bladder and lung cancer incidence for the US population. A modification by Gail et al. (1999) was used to obtain estimates of incidence within multi-year age strata, which itself would have associated uncertainty. The short time allotted for review is inadequate for a full examination of the appropriateness of the modified BEIR IV methodology used by USEPA (and a plethora of other potential issues). However, generally, the BEIR IV methodology for calculating excess risk is mathematically correct only when the specified response is mortality and mortality rates are used, not when the specified response is mortality and incidence rates are used, or when the specified response is incidence and incidence rates are used with BEIR IV equations which have not been appropriately derived for incidence. The beta or “b” value used by USEPA for *incidence* calculations at a given dose is based on *mortality* (pages 127, E-1), which is inappropriate. Additionally, BEIR IV equations are for mortality and may not be used for incidence without modification (i.e., derivation of appropriate BEIR IV equations specifically for incidence). This potential error is demonstrated in Appendix 1 to these comments. Although time did not allow for a more detailed review, USEPA does not indicate that any specific alterations were made to BEIR IV equations to account for incidence as the response. Therefore, TCEQ believes that USEPA may have used inappropriate BEIR IV methodology.

Some Practical Implications of Final Draft Arsenic SFO

USEPA’s Soil Screening Levels

The current USEPA regional screening level (RSL) for inorganic arsenic in residential soil is 0.39 mg/kg. The US Geological Survey reports the mean for arsenic in soil is 7.2 mg/kg (ATSDR 2007), and TCEQ uses a median background arsenic concentration for Texas soils of 5.9 mg/kg. Thus, the current residential soil RSL is already 18 times less than typical background soil arsenic concentrations. Adoption of the final draft SFO would reduce the current USEPA residential soil RSL by a factor of 17 to approximately 0.02 mg/kg at a conservative target excess risk level of 1 in 1,000,000. Even a residential soil RSL of 2 mg/kg corresponding to the upper end of the USEPA acceptable risk range (1 in 10,000) using the final draft SFO would be below typical background concentrations, making achievement of acceptable risk as defined by USEPA practically impossible at remediation sites. More importantly, this analysis would imply that typical naturally-occurring levels of arsenic in residential soil are unsafe for human contact.

In regard to individual excess lifetime cancer risk (IELCR), USEPA states on their website (<http://www.epa.gov/oust/rbdrm/sctrlsgw.htm>), “The IELCR represents the incremental (over background) probability of an exposed individual's getting cancer (i.e., a risk occurring in excess of or above and beyond other risks for cancer such as diet, smoking, heredity). Cleanup standards calculated on the basis of excess risk limits correspond to *allowable levels in excess of the background concentrations of the chemicals of concern normally present in the source media*” (emphasis added). Since regulatory agencies are concerned with regulating excess risk (i.e., risk over natural background), the risk due to

naturally-occurring background soil arsenic levels should be excluded from comparisons to the USEPA acceptable risk range. In effect, this is typically accomplished by USEPA acknowledging that although above the RSL or proposed remediation goal (PRG), soil arsenic levels at a remediation site are within background so no action is necessary in regard to arsenic. In a more strict sense, however, since per USEPA regulatory agencies calculate cleanup values based on excess risk over background, the soil RSL/PRG could be added to a representative background concentration to derive a comparison value which represents a regulatory acceptable level of excess risk (i.e., risk over background).

Implications for Food and Drinking Water Safety: Typical Dietary Exposure, Rice Consumption, Drinking Water, and Fish/Shellfish Consumption as Examples

A scientifically-defensible and realistic dose-response assessment for inorganic arsenic is critical given the grave implications of the final draft SFO for the US food and water supply. The examples below illustrate how estimates of risk due to dietary exposure to inorganic arsenic using the final draft SFO may have dire consequences on the perceived safety of US food and drinking water.

Typical Dietary Exposure

Using the final draft SFO for inorganic arsenic results in excess cancer risk estimates from dietary exposure exceeding the USEPA acceptable risk range (1 in 1,000,000 to 1 in 10,000). ATSDR (2007) reports the mean average US adult intake of inorganic arsenic is around 10.22 µg/day (range of 0.93-104.89 µg/day) based on a study (MacIntosh et al. 1997) which utilized residue data collected for the Food & Drug Administration Total Diet Study. Using the final draft SFO, excess calculated cancer risk would range from about 3.4 in 10,000 to 3.9 in 100, with an average calculated risk of about 3.8 in 1,000 due to dietary exposure. Even the calculated risk associated with the lower end of dietary inorganic arsenic exposure (3.4 in 10,000) would exceed the upper end of the USEPA acceptable risk range (1 in 10,000), and the calculated risk associated with the high end of dietary exposure would be 390 times the upper end of acceptable risk. Such analyses would imply that the US diet results in arsenic risk that is considered unsafe from a regulatory perspective.

Rice Consumption

In regard to eating rice specifically, the average excess risk for US adult (70 kg) rice eaters would be calculated at around 1.7 in 1,000 based on an average intake of 61.2 g dry rice/day (around 1 cup cooked) based on National Health & Nutrition Examination Survey data (Batres-Marquez and Jensen 2005) with 0.276 µg total arsenic/g US white rice and 27% of the total arsenic as inorganic arsenic (Williams et al. 2005). Even using a US adult average for rice intake that includes non-rice eaters (11.4 g dry rice/day) would still result in an excess risk of 3.1 in 10,000 for white rice, which exceeds the upper end (1 in 10,000) of USEPA's risk management range. Risk estimates would be higher for US brown rice than white rice due to a higher average percentage of total arsenic being inorganic (51%) (Williams et al. 2005), with average excess risk for US adult rice eaters being around 2.6 in 1,000 (26 times higher than the upper end of USEPA's risk management range). Such analyses would imply that rice and other food items (e.g., fish/shellfish) are unsafe for human. Consequently, there may be a potential for unwarranted advisories or warning labels on certain foods.

Drinking Water

Another implication of the draft final SFO is that the water used to prepare the rice (see example above) is itself by this calculation unsafe for human consumption. Drinking water in the US generally contains an average of 2 µg/L of arsenic (ATSDR 2007). Based on final draft SFO estimates, USEPA indicates that drinking water concentrations corresponding to 1 in 10,000 combined cancer risks for males and females are 0.21 and 0.14 µg/L, respectively. The implication is that on average all across the US, people's drinking water contains arsenic levels that exceed the upper end of the USEPA acceptable risk range (1 in 10,000) by approximately 10-14 times. In other words, on average, the level of arsenic in the nation's drinking water supply is unsafe.

For bladder cancer alone, the incidence risk calculated by USEPA based on final draft values for males/females is 3.1E-04 per µg/L. Therefore, based on 2 µg/L as an average drinking water concentration, the estimated bladder cancer risk for the US population would be 6.2 per 10,000 or 62 per 100,000. However, the actual occurrence of bladder cancer in the US is about 23 cases per 100,000 (males/females combined). It would take 3 times the actual bladder cancer incidence for US males/females combined to even make possible the 62 cases per 100,000 estimated due to arsenic exposure from drinking water alone. Thus, the incidence risk calculated by USEPA final draft values for bladder cancer appears to be inaccurate and overly conservative. Proceeding with this SFO will unnecessarily alarm the public by giving a greater perception of harm and risk than is actually taking place.

Fish/Shellfish Consumption

Shellfish and other marine foods contain the highest arsenic concentrations and are the largest dietary source of arsenic. Based on an FDA Total Diet Study, ATSDR (2007) reports that concentrations in canned tuna, fish sticks, haddock, and boiled shrimp were 0.609-1.470, 0.380-2.792, 0.510-10.430, and 0.290-2.681 mg/kg dry weight, respectively. The foods with the highest mean arsenic levels were haddock, canned tuna, fish sticks, shrimp, and fish sandwiches, with arsenic concentrations ranging from 0.568-5.33 mg/kg dry weight. Most recent studies show an arsenic concentration range of 0.82-37 mg/kg dry weight for fish (e.g., flounder, cod, sole, tuna), mussels, clams, oysters, shrimp, and blue crab, including fish, blue crabs, shrimp, mussels, and oysters from Texas (0.82-9.67 mg/kg) (see Galveston Bay/Gulf of Mexico results in Table 6-4 of ATSDR 2007).

The general consensus in the literature is that approximately 10% of the arsenic in the edible parts of marine fish and shellfish is inorganic arsenic (ATSDR 2007). A 10% adjustment to these reported arsenic levels in fish yields an inorganic arsenic concentration range of 0.029-3.7 mg inorganic arsenic/kg dry weight. Using the final draft SFO, a saltwater fish ingestion rate of 15 g/day (only two fish meals per month approximately), and an adult body weight (70 kg), the fish tissue concentration corresponding to the upper end of the USEPA acceptable risk range (1 in 10,000) is 0.017 mg inorganic arsenic/kg dry weight. The range of estimated inorganic arsenic levels in all these fish/seafood items (0.029-3.7 mg inorganic arsenic/kg) exceeds the fish tissue concentration calculated at the upper end of acceptable excess risk (1 in 10,000) using the final draft SFO. Regarding Texas specifically, the range of estimated inorganic arsenic levels in Galveston Bay/Gulf of Mexico seafood (0.082-0.967 mg/kg dry weight based on Table 6-4 in ATSDR 2007) is 5-57 times higher than the fish tissue concentration (0.017 mg/kg) calculated at the upper end of acceptable excess risk using the final draft SFO. These analyses would

imply that fish/shellfish in the US diet are unsafe for human consumption from a regulatory perspective. In turn, a determination of unacceptable risk due to arsenic in fish tissue would likely cause more waterbodies to be listed as impaired unnecessarily. As a result, there could be future inappropriate regulatory actions and unneeded expenditure of resources to investigate and try to reduce arsenic. There could also be negative public health consequences from such impairments, because fish consumption and the associated health benefits would decrease due to the false perception that arsenic is making fish unsafe to eat.

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Attachment C – TCEQ Comments on EPA Hexavalent Chromium Assessment

**Texas Commission on Environmental Quality
Comments Regarding the U.S. Environmental Protection Agency
Draft Toxicological Review of Hexavalent Chromium in Support of
Summary Information on the Integrated Risk Information System (IRIS)
Notice of Public Comment Period and Listening Session
75 FR 60454, September 30, 2010
Docket ID No. EPA-HQ-ORD-2010-0540**

On September 30, 2010, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register/Vol. 75, No. 189/Thursday, September 30, 2010/Notices) of a 60-day public comment period (ending November 29, 2010) for the, “Draft Toxicological Review of Hexavalent Chromium in Support of Summary Information on the Integrated Risk Information System (IRIS),” hereafter referred to as the draft assessment (EPA/635/R-10/004A). On November 10, EPA extended the comment deadline 30 days to December 29, 2010 (Federal Register/Vol. 75, No. 217/Wednesday, November 10, 2010/Notices). The draft IRIS assessment provides a draft oral slope factor (SFo of 0.5 per mg/kg-day) based on small intestine tumors in male mice in the National Toxicology Program (NTP 2008) drinking water study. The Texas Commission on Environmental Quality (TCEQ) has developed comments on the draft assessment to the extent practicable in the time allotted by EPA, focusing on the draft SFo, and provides the following comments for EPA consideration.

General Comments:

The assessment of the carcinogenic potential of hexavalent chromium (CrVI) has great implications in a regulatory context. Given their important role in the protection of public health, EPA regulatory risk assessors have a duty to perform the most scientifically-defensible assessments possible while giving careful and due consideration to comments and recommendations from other regulatory agencies, the public, external experts, stakeholders, etc. Although regulatory risk assessors have a penchant for erring on the side of health-protectiveness and conservative defaults, if erring on the side of conservatism significantly overestimates risk or hazard and is not fully justified, then harm to public health may result from diverting public, industry, and government attention and resources away from chemicals that may represent more of a public health risk at environmental levels. Therefore, TCEQ encourages EPA to give full, thoughtful, and careful consideration and evaluation to comments and recommendations from TCEQ, other regulatory agencies, the public, and external experts.

TCEQ is concerned that recent draft EPA assessments (e.g., dioxin, arsenic, formaldehyde) along with the draft CrVI assessment seem to demonstrate a pattern where the EPA timeline is sufficient for a less-than-desirable level of initial EPA analysis but insufficient: (1) for the public to be able to provide fully detailed comments on the many shortcomings of the draft assessments; (2) for EPA to seriously and meaningfully evaluate the scientific merit of public comments; (3) for EPA to conduct the additional analyses required to fully respond to public comments and appropriately revise the draft assessment based on the scientific merit of comments; and (4) for EPA to conduct the fully credible, balanced, and transparent assessment the public deserves where the effects of the significant uncertainties associated with certain key decisions and procedures are fully examined qualitatively and quantitatively. Such shortcomings undermine the confidence of States and other parties who often rely on EPA toxicity factors

and over time, will tend to marginalize EPA in terms of a reliable source for scientifically objective, defensible, and predictive toxicity factors. This may be one reason States are progressively deriving more toxicity factors as opposed to relying on EPA assessments, which often rely heavily on a penchant for default procedures representing a seemingly nonobjective and insurmountable hurdle for alternative analyses strongly supported by data (e.g., nonlinear dioxin carcinogenicity assessment, cytotoxicity-induced regenerative cell proliferation carcinogenic mode-of-action (MOA) for formaldehyde-induced respiratory tract cancer).

90-Day Comment Period:

The 90-day comment period is insufficient for regulatory agencies and others to provide the most thorough and meaningful comments possible based on an in-depth review and analysis of the draft IRIS assessment. There is great complexity associated with multiple issues relevant to the assessment of CrVI risk and hazard. The draft IRIS assessment alone is 300 pages, and there are hundreds of pages (at a bare minimum) of other documents and studies relevant to the assessment of CrVI risk and hazard. Given the complexity and volume of relevant materials, it is impracticable for EPA to expect detailed specific comments from external experts given the short period allowed for a critical review of the draft assessment and more specifically, the procedures, calculations, and supporting arguments employed by EPA therein. Given that external experts cannot devote all their time to review and comment, the 90-day comment period only allows a superficial review of the draft assessment at best, leads to a less-than-desirable level of transparency and peer review, and undermines confidence in the process. Consequently, TCEQ is only able to provide comments based on a cursory review. If EPA seeks more detailed and meaningful public input and technical comments, at a minimum EPA should extend the comment period at least 30 days past the December 29 deadline to allow stakeholders to: (1) perform a more detailed review of the volumes of relevant information; (2) more fully examine statistical procedures and the rationale and scientific support for key EPA decisions and analyses; and (3) provide more detailed specific comments on all problematic issues associated with the draft IRIS assessment.

Toxicology-Based Comments:

Biological Plausibility of a Mutagenic Carcinogenic MOA and Exceedance of the Mouse Gastrointestinal (GI) Tract Reductive Capacity

EPA's conclusion that mutagenicity (and consequently carcinogenicity) can occur at doses within GI reductive capacity relied on an entirely speculative mouse reductive capacity, flawed arguments, and is not scientifically sound. When discussing data supportive of the hypothesized mutagenic MOA for CrVI (and default linear, low-dose extrapolation by corollary), EPA admits that overwhelming the GI reductive capacity of the mouse is a plausible explanation for CrVI-induced genotoxicity following sufficiently high mouse oral exposure. By corollary, overwhelming the mouse's GI reductive capacity is a plausible explanation for CrVI-induced carcinogenicity in the NTP (2008) drinking water study. However, EPA wholly rejects this "plausible explanation" (p. 207) since, "there are inconsistencies."

Firstly, all studies are rarely (if ever) 100% consistent, and lack of 100% consistency does not preclude sound conclusions based on best scientific judgment and consideration of all relevant data in a weight of evidence approach. For example, there are inconsistencies with CrVI being genotoxic *in vivo* and *in vitro*

since not all results are positive (see Tables 4-23 and 4-21 of draft assessment), but this certainly does not (and should not) preclude EPA from concluding that CrVI is genotoxic (see Section 4.7.3.4).

Secondly, as evidence that exceedance of the mouse GI reductive capacity is not required for genotoxicity and carcinogenicity, EPA indicates that: (1) the average rate of CrVI exposure at even the highest dose in the NTP (2008) study was within the “estimated” reductive capacity of the mouse GI tract; (2) Devi et al. (2001) found positive genotoxicity results in leukocytes at doses > 10-fold lower than those used in the NTP study and within the “estimated” reductive capacity of the mouse; and (3) Stout et al. (2009) did not find an upward inflection (threshold) point in nonlinear data (tissue concentration and/or mouse small intestine neoplasm data) as evidence of where dose may have saturated reductive capacity. However, regarding (1) above, *the “estimated” mouse GI reductive capacity is entirely speculative* (scaling from humans to mice with body weight (BW^{3/4})). In fact, EPA elsewhere (p. 211) states, “data are not available for the reductive capacity of the mouse.” Regarding (2), the Devi et al. (2001) study was an oral gavage study while the speculative GI reductive capacity was calculated on an hourly basis. Thus, *a direct comparison of the speculative hourly mouse reductive capacity and the bolus doses in the Devi et al. gavage study is not appropriate*. Additionally, the positive results for leukocytes examined in Devi et al. (2001) are of questionable relevance for the carcinogenic MOA compared to the entirely relevant negative genotoxicity findings in the cancer target tissues examined in De Flora et al. (2008). *The DNA damage demonstrated by Devi et al. (2001) in mouse leukocytes does not result in cancer-causing mutations in that tissue, much less demonstrate how CrVI causes cancer in actual target tissues where De Flora et al. (2008) did not find DNA damage, even at drinking water concentrations 50 and 200 times the federal maximum contaminant level (MCL) (i.e., “brightly yellow” levels)*. Regarding (3) above, Stout et al. (2009) also relied upon the speculative mouse GI reductive capacity to conclude that the absence of an upward inflection point in nonlinear data did not support a threshold. However, as the “estimated” mouse reductive capacity is entirely speculative, no scientifically sound conclusions can be made by Stout et al. (2009) or EPA based on it. *It is more plausible that all doses exceeded actual mouse GI reductive capacity (see TCEQ comments below)*. Therefore, all data used by Stout et al. are from points on the dose-response curve higher than the inflection point, making the observance of an inflection point impossible. *Contrary to the draft assessment, EPA cannot make sound scientific conclusions concerning the relationship between GI reductive capacity and the potential for genotoxicity and/or carcinogenicity in the absence of actual mouse GI reductive capacity data or similarly informative data.*

Overwhelming the reductive capacities of the mouse and rat GI tracts remains a plausible explanation for the carcinogenicity observed in NTP (2008). There are data which are informative concerning whether or not mouse GI reductive capacity was exceeded at the NTP (2008) study doses. More specifically, NTP (2007) provides evidence of CrVI absorption in mice at around 10 mg/L and higher in drinking water (see blood results in Table G1), but not at lower doses. This evidence strongly suggests that GI reductive capacity was exceeded by all mouse doses (14.3-267 mg/L) in the NTP (2008) study. In regard to rat reductive capacity and the oral carcinogenicity observed in NTP (2008), NTP (2007) (see blood results in Table G1) and Sutherland et al. (2000) provide evidence of CrVI absorption in rats at around 10 mg/L and higher in drinking water, but not at lower doses. Similar to the mouse, these rat results strongly suggest that reductive capacity was exceeded by all rat doses (14.3-516 mg/L) in the NTP (2008) study. *Thus, for both mice and rats, EPA had data strongly suggesting that NTP (2008) doses exceeded GI reductive capacity*. Had the NTP (2008) doses associated with 14.3-516 mg/L truly been within actual GI reductive capacity, CrVI would have been effectively reduced to CrIII and significant absorption into the

bloodstream would not have occurred in NTP (2007) at water levels around ≥ 10 mg/L. Instead of relying on these actual data, EPA relied on a speculative mouse reductive capacity estimate to make a key decision and conclude that mutagenicity (and consequently carcinogenicity) can occur at doses within the GI reductive capacity. *For EPA to admit that overwhelming the reductive capacity of the mouse GI tract was likely responsible for the carcinogenicity observed in NTP (2008) would inconveniently put EPA off the linear, low-dose extrapolation pathway with issues EPA is ill-prepared to address quantitatively within this carcinogenic assessment (e.g., doses at which the mouse and human GI reductive capacities are exceeded (thresholds for carcinogenicity), human relevance of the mouse tumors given exceedance of the mouse GI reductive capacity and given truly environmentally relevant lifetime human doses), especially given the lack of data necessary to address some of these issues (e.g., lack of species-specific GI reductive capacity data).*

The above comments highlight serious shortcomings in EPA's story about exceedance of the mouse GI reductive capacity not remaining a plausible explanation for CrVI-induced genotoxicity and subsequent carcinogenicity. EPA's discussion fails to adequately support their conclusions concerning study doses not exceeding mouse GI reductive capacity. TCEQ notes that for EPA to acknowledge this explanation would be contrary to their use of default linear, low-dose extrapolation (i.e., no biological threshold for CrVI mutagenicity based on stomach/GI reductive capacity) and call into question the human relevance of the mouse tumors observed.

Human Relevance of the Mouse Tumors

The small intestine neoplasms in mice (and oral cancers in rats) observed in NTP (2008) are of questionable relevance to humans. Reasons include: (1) mouse GI reductive capacity may have certainly been exceeded (e.g., there are no actual mouse GI reductive capacity data, blood data from NTP (2007) suggest that NTP (2008) doses exceeded GI reductive capacity); (2) epidemiological worker data are not supportive; and (3) the NTP (2008) study doses are not relevant to the truly low, typical environmental doses. The issue in (1) was discussed in TCEQ comments above.

Regarding (2), *epidemiological worker data do not support elevated GI cancer risk.* A meta-analysis of thirty-two CrVI worker studies (Gatto et al. 2010) showed no significant increase in GI tract cancers (although a much smaller highly-exposed subgroup had slightly elevated esophageal cancer). Additionally, none of the studies reported statistically elevated oral cavity or small intestine risk. For example, the meta-analysis included GI tract cancer data obtained from the study authors of Luippold et al. (2003) and Gibb et al. (2000), which did not show excess cancers of the GI tract (e.g., stomach, oral). This information is relevant since workers can be exposed to air concentrations sufficiently high that ingestion is significant. For example, 48% and 39% of the chromate workers in Public Health Service (PHS 1953) had yellow tongues and teeth, respectively. Yellow tongues and teeth were not attributable to smoking and yellow tongue scrapings contained chromium (see pp. 76-77 and Figures 10 and 11 of PHS 1953). While this discoloration was due to the ingestion of relatively high oral doses of CrVI by these workers, no excess GI cancers were found in PHS (1953) or in Luippold et al. (2003) or Gibb et al. (2000), which evaluated some of the same workers. Regarding a comparison between worker and NTP (2008) study doses, Gatto et al. (2010) estimated a daily worker oral dose of 0.004 mg/kg-day, which could vary by an order of magnitude in either direction depending on cohort-specific air concentrations and particulate size/solubility. The doses that produced small intestine cancers in mice (and oral cancers

in rats) in NTP (2008) are orders of magnitude higher than this estimated occupational oral dose (whether +/- an order of magnitude). The difference in GI cancer outcome between NTP (2008) and Gatto et al. (2010) and these other worker studies could be that although workers were exposed to estimated oral doses significantly higher than typical environmentally relevant doses, exposure was within the GI reductive capacity of the workers as opposed to the laboratory mice/rats in NTP (2008) exposed to significantly higher doses beyond their GI reductive capacity. *The bottom line is that even in occupational workers exposed to sufficiently high air levels of CrVI as to produce (via ingestion) yellow tongues and teeth in 39-48% of the workers, PHS (1953) looked for but did not find excess GI cancers or any cancer excesses outside the respiratory tract (see p. 56 of PHS 1953), and these study results are supported by other studies as well (e.g., Gatto et al. 2010, Luippold et al. 2003, Gibb et al. 2000).*

In regard to (3), *the NTP (2008) study drinking water doses are not relevant to humans.* For example, the mouse doses (0.38-8.7 mg/kg-day) are 130-3000 times higher than the human adult dose ($(0.1 \text{ mg/L} \times 2 \text{ L/day})/70 \text{ kg} = 0.0029 \text{ mg/kg-day}$) at the federal MCL. CrVI drinking water concentration data from Midland, Texas, have been used recently to suggest that the NTP (2008) doses are relevant to human exposures since the lowest cancer-producing dose from the NTP study scaled to humans using $BW^{3/4}$ (0.166 mg/kg-day) is comparable to the estimated human dose at the maximum detected concentration (5.41 mg/L) in Midland (0.155 mg/kg-day) (Collins et al. 2010). However, this comparison is erroneous for several reasons. The NTP (2008) study is a lifetime exposure study where laboratory animals were exposed to a constant concentration in drinking water. By contrast, based on community input to TCEQ, some people in the affected area in Midland were already drinking bottled water due to generally poor water quality (e.g., high total dissolved solids). Additionally, others stopped drinking the water as CrVI concentrations began to rise and the water began to turn yellow around ≥ 1 ppm, which was indicated in the source (TDSHS 2009) cited by Collins et al. (2010) but which the authors for some reason failed to mention. Consequently, public exposure was for far less than a lifetime. Also, although exposure concentrations changed over time, they were significantly lower than the maximum concentration assumed by Collins et al. (2010). Thus, this comparison by Collins et al. (2010) is based on erroneous assumptions in a failed attempt to demonstrate the human relevance of the NTP study doses. Although there is significant uncertainty in how water concentrations changed over time, a more reasonable worst-case scenario might be: $0.7 \text{ mg CrVI/L (average)} \times 2 \text{ L/day} \times 5 \text{ years}/70 \text{ years} = 0.0014 \text{ mg/kg-day}$, which is over 110 times less than the lifetime average mouse dose cited by Collins et al. (2010). *The doses on NTP (2008) are hundreds or thousands of times higher than typical environmentally relevant doses. Therefore, for this and other reasons discussed, study results and the draft SFO are of questionable utility and predictive ability for use in risk assessment.*

Disparate EPA Scientific Standards

EPA appears to hold a higher standard for the scientific defensibility of data that do not support a default or pre-determined EPA assessment pathway. For example, in discussing the hypothesized mutagenic carcinogenic MOA, EPA did not consider the De Flora et al. (2008) drinking water study data to be informative about genotoxicity in the cancer target tissues because it was only for 9 months, although it is still a chronic study and genotoxicity/mutagenicity would be expected early in the carcinogenic process if a CrVI produces cancer through a mutagenic MOA. These data would lend weight against a mutagenic MOA and subsequent linear, low-dose extrapolation. Conversely, EPA judged comparisons of entirely speculative estimates of mouse GI reductive capacity to various study doses (e.g., Devi et al. 2001, Stout

et al. 2009) as sufficient to conclude that genotoxicity/mutagenicity can occur at doses within GI reductive capacity, which is needed to justify the absence of a threshold and to assert use of linear, low-dose extrapolation. EPA's selection of relevant study data reflects a bias, where data supporting EPA's default linear, low-dose extrapolation are considered sufficiently conclusive and any data not supporting that approach are dismissed.

In addition to the comments above pertaining to an example of apparent disparate standards applied to data within the CrVI assessment, *there appears to be inconsistency across assessments regarding the data deemed by EPA to be sufficient to support the direction of an assessment.* For example, using EPA's apparent standard of "inconsistency" as applied to data concerning exceedance of GI reductive capacity in the current assessment as sufficient to discount a certain hypothesis as unsupported (i.e., existence of a biological threshold for CrVI mutagenicity/carcinogenicity based on GI reductive capacity), it is abundantly clear that EPA should have never derived a unit risk factor (URF) for Hodgkin lymphoma and leukemia for formaldehyde in the 2010 draft assessment. Only a minority of epidemiological data support a link, the hypothesized MOA is highly speculative and biologically implausible (e.g., Lu et al. 2010), EPA indicates that there is no way to derive a meaningful URF for environmental exposure where risk is determined by environmentally irrelevant peak exposures, there is no dose-response relationship between cumulative exposure and risk that might have produced a meaningful URF, and yet EPA derived a formaldehyde URF for non-Hodgkins lymphoma and leukemia not only in the midst of inconsistency but of scientific indefensibility. *Disparate standards are even applied by EPA to the same data depending upon whether they support default assessment procedures.* For example, in the 2010 draft dioxin reanalysis, EPA judged AhR-mediated MOA data to sufficiently support the biological plausibility of dioxin being a known human carcinogen, but judged the same MOA data as insufficient to justify the corollary nonlinear carcinogenic assessment. *Overall, this appears to lend support to the existence of a double standard where a high standard is applied to data contrary to a pre-determined path (e.g., EPA's treatment of De Flora et al. 2008 in the CrVI genotoxicity discussion), requiring only the interjection of some level of ever-present uncertainty for rejection, while a lower standard is used to judge data that justify the default or desired path (e.g., EPA's treatment of Devi et al. 2001 and Stout et al. 2009 in the discussion of CrVI GI reductive capacity, EPA's hypothesized MOA and derivation of formaldehyde URFs for Hodgkin lymphoma and leukemia, EPA's treatment of the formaldehyde BBDR model).*

In effect, the unequal treatment of data results in "cherry-picking" data, an unbalanced and biased approach towards risk assessment, and undermines user and public confidence. *The same standard should be applied to data regardless of whether or not they support a EPA default procedure or preferred assessment pathway (e.g., linear, low-dose extrapolation based on an assumption of no threshold).*

Bioavailability

Serious issues exist regarding the predictiveness of the draft SFo given likely differences between the bioavailability in mice (and rats) at the doses used in NTP (2008) and in humans at typical environmentally relevant doses. In regard to the bioavailability of CrVI, TCEQ notes that the human study cited by EPA where as high as 10% of CrVI was absorbed (Kuykendall et al. 1996) involved a bolus dose 25 times higher than the dose associated with consuming 2 liters of drinking water all at once at the current MCL. The limited human bioavailability at the high bolus dose used raises serious questions about the bioavailability at much lower, environmentally relevant doses (e.g., lower, non-bolus doses).

Additionally, the rodent data cited by EPA are of little relevance for proving bioavailability in humans at environmentally relevant doses as the rodent doses cited (p. 210) were very high on a body weight basis and human GI reductive capacity is expected to be different. Humans and mice are likely to differ in GI reductive capacity (a likely important determinant of risk) due to several factors such as varying stomach pH, fluid production rates, food content, and emptying and Cr reduction rates. For example, the human fasted stomach pH is around 2-3 times less than that of the mouse and rat (McConnell et al. 2008, Ruby et al. 1996), which would be expected to be associated with a greater human CrVI reductive capacity. *The differences between the bioavailability in mice (and rats) at the doses used in NTP (2008) and in humans at typical environmentally relevant doses would have to be quantitatively accounted for to derive a scientifically defensible and predictive SFO for regulatory decision making.* This is especially critical considering that the NTP (2008) doses likely exceeded the mouse (and rat) GI reductive capacity (see TCEQ comments above).

Genotoxicity versus Mutagenicity

EPA appears to inappropriately automatically equate and discuss genotoxicity data as direct evidence of mutagenicity. While evidence of genotoxicity certainly has bearing on potential mutagenicity and is important supportive information under EPA guidelines (EPA 1986, 2007), it is not direct evidence of the generation of mutations as seemingly characterized by EPA in the draft CrVI assessment. EPA guidelines on mutagenicity risk assessment (EPA 1986) concern *heritable* mutagenic changes, and not all carcinogenic chemicals that are capable of interacting with DNA will have a mutagenic MOA for cancer (EPA 2007). EPA discusses no positive *in vivo* data for mutagenicity in cancer target tissues in oral animal studies, only genotoxicity data (e.g., DNA-protein crosslinks, DNA strand breaks) in non-target tissues of unknown relevance to the tumors observed in NTP (2008) which EPA inappropriately automatically equates and discusses as direct evidence of mutagenicity (see first paragraph p. 204). This *in vivo* genotoxicity discussed by EPA does not result in cancer-causing mutations in those tissues (e.g., liver, leukocytes), much less explain how CrVI causes cancer in actual target tissues for which existing genotoxicity data (De Flora et al. 2008) are negative.

Interspecies Scaling

The interspecies scaling used by EPA should be fully justified. The draft SFO was calculated using $BW^{3/4}$ scaling from mice to humans (p. 229). The tumors observed in mice (small intestine tumors) were portal-of-entry (POE) and not systemic in nature. EPA (2005) is unclear as to whether the data which support this adjustment include POE tumor data. *EPA should fully justify use of $BW^{3/4}$ scaling for this purpose or conduct no such adjustment, especially given that humans and mice are likely to differ in GI reductive capacity (see TCEQ comments above).*

Imminent Generation of Data Critical to the Carcinogenic MOA Analysis

TCEQ strongly urges EPA to postpone finalizing the draft CrVI assessment as the generation of new data critical to understanding the carcinogenic MOA is imminent. Unlike the typical situation where regulatory agencies are asked to delay an assessment for years pending results of a study which might be informative, study data are currently being generated that are directly relevant and critical to a scientifically defensible carcinogenic MOA analysis by EPA. The overall goal of the CrVI MOA Research Program is to understand the contribution of different potential carcinogenic MOAs for CrVI

(e.g., genotoxicity, cytotoxicity, inflammation, oxidative stress) across a broad range of doses in order to provide both statistical and biological understanding of potential thresholds for CrVI carcinogenicity. The contributions of various MOAs over a range of doses will be determined by a combination of genome-wide microarray analyses in intact animals, high data content imaging of activation of key DNA-damage pathways, and consideration of dose dependencies in dosimetry. These data may elucidate the shape of the rodent dose-response curve and the human relevance of these responses prior to development of the final SFO. Detailed information may be found at <http://www.tera.org/Peer/Chromium/Chromium.htm>. All technical manuscripts are expected to be completed no later than the end of the 2nd quarter, 2011, before the final assessment is due in the 3rd quarter (http://cfpub.epa.gov/ncea/iristrac/index.cfm?fuseaction=viewChemical.showChemical&sw_id=1107). *The data to be generated by the*

CrVI MOA Research Program will address many important MOA data gaps (see the Appendix) and are of paramount importance to a scientifically rigorous CrVI carcinogenic assessment. These data may help explain such issues as why the mutagenic MOA hypothesized in the draft assessment (even at exposures below the GI reductive capacity) would predict GI tumors in highly orally-exposed workers (PHS 1953) and in multiple tissues in the NTP (2008) study but in fact such tumors did not occur. Additionally, they may explain more convincingly than the draft assessment (Section 4.7.3.3) why intestinal tumors only occurred in animals with prolonged hyperplasia, or may support an alternative carcinogenic MOA as much more plausible (e.g., Thompson et al. 2010). TCEQ strongly encourages EPA to utilize these data to inform the carcinogenic MOA analysis and revise the draft assessment as justified (even if the EPA timeline is pushed farther out) as opposed to viewing these important data as an inconvenient late development in the assessment process and simply interjecting some level of uncertainty and proceeding down the previously prescribed path.

Implication-Based Comments:

While significant implications themselves do not speak to the scientific defensibility of the draft SFO for CrVI, they emphasize the critical importance of deriving the most scientifically defensible, biologically relevant, and predictive toxicity factors possible.

Health-Protective Environmental Media Levels

Because the draft SFO for CrVI is relatively high, there are important implications for the calculation of health-protective environmental media levels such as EPA surface soil preliminary remediation goals (PRGs) and the MCL. Soil PRGs for CrVI may decrease by a factor of 10 or more even without the use of age-dependent adjustment factors (ADAFs). Soil PRGs will be at the low end of the range of background chromium soil levels (US mean of 37 mg/kg, ATSDR 2008), with a residential PRG of 0.29 mg/kg and a commercial/industrial PRG of 5.6 mg/kg. Soil CrVI PRGs within background chromium levels will require costly remediation site-specific soil studies to differentiate between CrVI and other forms (e.g., CrIII) at all sites where it is a chemical of potential concern (COPC).

The draft SFO also has significant implications for the federal drinking water MCL. *Using the EPA acceptable risk range (1E-06 to 1E-04) and draft SFO, the MCL would need to be from 0.07 to 7 ppb (without use of ADAFs) for adequate protection of public health. Compared to the current MCL of 100 ppb, this represents approximately a 14-1,400 fold decrease. With typical US drinking water supplies containing total chromium levels within a range of 0.2 to 35 ppb (most supplies < 5 ppb, ATSDR 2008), a*

new MCL for total chromium of 0.07-7 ppb conservatively based on the draft SFO could be exceeded on a wide basis depending upon the target risk level used. If a CrVI-specific MCL is promulgated, water suppliers would have to begin analyzing for chromium using a method that can speciate forms and one sensitive enough to detect chromium at concentrations much lower than now required to demonstrate compliance with the current MCL. Available analytical methods do not appear to be capable of detecting CrVI at the lower end of the potential new MCL range (ATSDR 2008). *A new MCL may be problematic for many public drinking water supplies.* For example, a recent California drinking water survey showed that 14% of drinking water sources had concentrations of ≥ 10 ppb CrVI (ATSDR 2008), which is above the potential new MCL range of 0.07-7 ppb based on the EPA acceptable risk range and the draft CrVI SFO. Additionally, based on a review of treatment removal technologies, process-efficient and cost-effective methods for CrVI removal from drinking water supply sources appear to be lacking (Sharma et al. 2008).

Closing Remarks:

TCEQ acknowledges the significant agency effort and resources required to produce draft toxicological assessments, review public comments, and make scientifically justified revisions and additions. The public deserves regulatory agencies to be able to make good risk management decisions using realistic risk estimates based on the most scientifically defensible and predictive toxicity factors possible, not based on toxicity factors of uncertain predictive ability that are just conservative by default. Consequently, for this and other draft assessments, TCEQ urges EPA to give thoughtful scientific and common-sense consideration to these and other comments and the weight of scientific evidence which supports or contradicts key decisions and procedures employed in the draft EPA assessment. Agreement with the ultimate final SFO value necessarily implies agreement with its ability to reasonably predict risk at commonly encountered, environmentally relevant doses, and agreement with the unavoidable conclusions about public health that will naturally follow from risk estimates based on the SFO. Additionally, TCEQ encourages EPA to postpone finalizing the draft assessment as necessary since the generation of new data which will address important MOA data gaps is imminent through the CrVI MOA Research Program. Appropriate consideration and incorporation of these data would result in a more scientifically rigorous CrVI carcinogenic assessment.

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Attachment D – TCEQ Comments on EPA Dioxin Interim Preliminary Remediation Goals

**Texas Commission on Environmental Quality
Comments Regarding the U.S. Environmental Protection Agency
Draft Recommended Interim Preliminary Remediation Goals for Dioxin
in Soil at CERCLA and RCRA Sites
Notice of Availability and Announcement of Public Comment Period
75 FR 0984, January 7, 2010
Docket ID No. EPA-HQ-SFUND-2009-0907**

The Texas Commission on Environmental Quality (TCEQ) provides the following comments on the U.S. Environmental Protection Agency (EPA) announcement of the public comment period regarding its proposal to adopt interim preliminary remediation goals (PRGs) applicable to dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)) and other dioxin-like compounds in soils at Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA / Federal Superfund) and Resource Conservation and Recovery Act (RCRA / Federal Hazardous Waste) corrective action sites.

EPA proposes to substantially reduce the PRGs for dioxin in residential soils from the present value of 1 part per billion (ppb) TCDD toxicity equivalents (TEQ) to .072 ppb TCDD TEQ. For dioxin in soils at commercial/industrial sites, EPA proposes to reduce the PRG from a level within the concentration range from 5 to 20 ppb TCDD TEQ to .950 ppb TCDD TEQ. EPA expects to finalize these revised PRGs in June 2010 and that they will remain in effect in the interim until it issues the final reassessment of dioxin toxicity which it plans to accomplish by the end of 2010. EPA intends to then issue updated PRGs based on its final dioxin reassessment and to reevaluate cleanup decisions that were based on these 2010 interim PRGs in order to ensure that those cleanups remain protective of human health.

Toxicology-Based Comments:

The TCEQ provides the following comments which question the rationale for issuing revised PRGs for dioxins in soils until such time as scientifically defensible toxicity values are available upon completion of the dioxin reassessment.

- The complexity of the analysis of dioxin toxicity, the unknown outcome of the final dioxin reassessment, and the potential for significant implications associated with the interim PRGs, all indicate that EPA should allow a longer comment period for stakeholders to prepare comments. The allotted 50 days to prepare comments does not provide for an appropriate level of peer review and undermines confidence in the interim PRG values. At a minimum, EPA should extend the comment period at least 60 days past the February 26 deadline to allow stakeholders to perform a more detailed review of the volumes of relevant information and to comment on problematic issues associated with the interim PRG calculations.
- The draft interim PRG document states that the proposed interim PRGs are informed by the best available science at this time.¹ The document negates this claim when it also states “there is uncertainty associated with these draft recommended interim PRGs because they do not take into account peer review comments on the new science that was reviewed by the National Academy

¹ Page 2, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

of Sciences (NAS), and new science that was released since the NAS review.”² This contradiction calls into question the transparency of the PRG development process. The proposed interim PRGs are not based on the best available science at this time. Specifically, the carcinogenic oral slope factor (SFo) (EPA, 1985) and the non-carcinogenic chronic minimum risk level (MRL) (ATSDR, 1998) toxicity factors used in the PRG calculations are 25 and 12 years old, respectively. Also, the proposed interim PRGs do not take into account the National Toxicology Program (NTP) animal studies (NTP, 2004 and 2006) released after the 2003 draft reassessment. The final dioxin reassessment will provide a better basis for revised PRGs provided the recommendations from the NAS are appropriately incorporated into the final analysis (e.g., incorporation of nonlinear and probabilistic approaches, quantitative characterization of uncertainty and variability in risk, transparency in selection of key data, and assessing dose-response model goodness of fit). The TCEQ concludes that there is sufficient uncertainty regarding dioxin toxicity that EPA should not issue revised dioxin PRGs until all stakeholders have had an opportunity to help determine the best science available at this time.

- EPA did not include the 2007 California EPA SFo³ used for the draft drinking water public health goal (CalEPA, 2007) when discussing the available SFo values for use in PRG calculations. The CalEPA’s 2007 SFo is based on a 2004 NTP study (NTP, 2004) and is the only SFo available that is informed by the latest science. The CalEPA and others consider that study to be a superior basis for SFo calculations, due to its careful design and conduct and the improved survival rate, as compared to the 1978 Kociba study (Kociba RJ, Keyes DG, Beyer JE, et al., 1978) adopted by EPA for its 1985 SFo⁴ and used in the interim PRG calculation. The CalEPA’s 2007 SFo is six times less conservative than the EPA’s 1985 SFo and is based on the latest and perhaps best animal study conducted to date for carcinogenic risk assessment.
- The monkey study (Schantz SL, Ferguson SA, Bowman RE., 1992) data which serve as the basis of the 1998 non-cancer toxicity factor⁵ (ATSDR, 1998) used by EPA for the interim PRG calculations were excluded from the quantitative assessments of tolerable daily intakes by several international agencies.⁶ Substantial amounts of non-TCDD compounds (e.g., polychlorinated dibenzo-p-dioxins, polychlorinated dibenzo-p-furans, and dioxin-like polychlorinated biphenyls (PCBs)) were found to be contributing to the TCDD TEQ concentrations for several of the TCDD-exposed monkeys and other non-exposed monkeys (Alward LL, Lakind JS, Hays SM., 2008). Use of the daily dose of TCDD from this study to derive the chronic MRL is problematic, since that value likely underestimates the TCDD TEQ concentration that was present at the time of the observed effects.
- EPA should develop a reasonable estimate of relative bioavailability (less than 1) of soil dioxin from available studies and then use that value in the PRG calculations. EPA assumes the dioxin bioavailability from soil is the same as the dioxin bioavailability in the toxicological studies used as the basis for the toxicity factors, i.e., the SFo and chronic MRL.⁷ EPA’s use of a relative bioavailability of 1 in the interim PRG calculations⁸ demonstrates this assumption, which is

² Page 4, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

³ 26,000 per mg/kg-day

⁴ 156,000 per mg/kg-day

⁵ ATSDR’s chronic MRL

⁶ Joint Expert Committee on Food Additives (JECFA) of the World Health Organization (WHO) and Food and Agricultural Organization (FAO), European Commission Scientific Committee on Foods (ECSCF), and United Kingdom Committee on Toxicity (UKCOT).

⁷ Page 11, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

⁸ Pages 23-24, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

questionable since animals in toxicological studies are typically dosed with more bioavailable forms of chemicals than those occurring in soil.

- The draft interim PRG document⁹ also mentions that EPA is requesting comments on the utility of alternative PRGs at a 1E-06 excess cancer risk level. The above comments also apply to these alternative PRGs with the additional concern that setting PRGs within or below background concentrations is not feasible from a compliance perspective. Such an approach could result in costly studies to determine site-specific background concentrations whenever TCDD or other dioxin-like compounds are present at a site.

Implementation-Based Comments:

The TCEQ provides the following implementation-based comments which conclude that

EPA should not issue revised PRGs for dioxin and dioxin-like compounds in soils until such time as it completes the final reassessment of dioxin toxicity. However, if EPA decides to issue the interim PRGs, then it should, previously or concurrently, release additional guidance that more specifically discusses how the interim PRGs are to be applied to active and closed dioxin sites. Also, EPA should clarify in such guidance that it does not intend to use revised PRGs, prior to its completion of the final dioxin reassessment and issuance of associated PRGs, to conclude that any site that has been appropriately evaluated and/or remediated in response to its 1998 dioxin PRGs requires additional response to be protective of human health.

- EPA is not being consistent with its own logic presented in the 1998 Office of Solid Waste and Emergency Response (OSWER) memorandum which memorializes the dioxin cleanup levels historically used by EPA at CERCLA and RCRA cleanup sites. That memorandum states, “The Office of Solid Waste and Emergency Response does not believe it is prudent to establish new, and possibly varying, precedents for Superfund or RCRA dioxin levels just prior to the release of this reassessment report.” (EPA, 1998). The TCEQ concurs with EPA’s previously stated view that it should not release interim PRGs just prior to the release of the final dioxin reassessment.
- EPA states that it intends to issue interim PRGs for dioxin this June and that it expects to complete the dioxin reassessment by the end of 2010. If this is the case, then the TCEQ questions the purpose and utility of EPA issuing interim PRGs when those PRGs are likely to change, after being reassessed, in only six or seven months. On the other hand, when EPA stated its expectation to complete the dioxin reassessment by the end of 2010, it also stated that completion by that date was “subject to further consideration of the science and the scope and complexity of the revisions that will need to be made.”¹⁰ EPA has been working since 2004 to incorporate the comments provided by the NAS with regard to its last version of the dioxin reassessment issued in 2003. When EPA issues its proposed final dioxin reassessment, it should expect comments regarding whether it has appropriately addressed the concerns expressed by the NAS in 2004 and whether new research regarding dioxin toxicity has been appropriately incorporated into the reassessment. So it seems reasonable to expect that EPA will need more time, and perhaps significantly more time, beyond the end of 2010 to complete the dioxin reassessment. In this circumstance, the TCEQ objects to the issuance of interim PRGs for dioxin in soils that are not based on the best science currently available and that could remain in effect for an unknown

⁹ Page 13, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

¹⁰ Page 1, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

number of years. Both of these possible circumstances support the conclusion that EPA should wait until the final dioxin reassessment is completed before it issues revised PRGs for dioxins.

- The discussion that EPA provides on implementation issues in the public review draft of the recommended interim PRGs for dioxins in soils does not provide sufficient detail for stakeholders to be able to evaluate how EPA intends to use the revised PRGs. Additional detail is needed which describes how EPA intends its regions to reevaluate CERCLA and RCRA corrective action sites that have been evaluated and/or remediated in the intervening period between its issuance of the interim PRGs and the final PRGs that are to be consistent with the final dioxin reassessment. Also, the document does not discuss whether EPA intends to use the interim PRGs when it reevaluates CERCLA and RCRA corrective action sites that have been evaluated and/or remediated using its 1998 PRGs.¹¹ However, EPA does mention that its regions should “consider” this public review draft document on the recommended interim PRGs when performing five-year-reviews of CERCLA sites containing dioxin or dioxin-like compounds to determine whether the original remedy stated in the Record of Decision remains protective. EPA should release additional guidance no later than the issuance of any interim PRGs that more specifically discusses how the interim PRGs are to be applied to active and closed dioxin sites. This guidance should specifically address how PCB sites that have only Arochlor data, and for which TCDD TEQs cannot be calculated, are to be handled. Also, EPA should clarify in this guidance that it does not intend to use the interim PRGs, prior to its completion of the final dioxin reassessment, to conclude that any site that has been appropriately evaluated and/or remediated in response to its 1998 dioxin PRGs requires additional response to be protective of human health.

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¹¹ Pages 2, 14-16, www.epa.gov/superfund/policy/remedy/pdfs/Interim_Soil_Dioxin_PRG_Guidance_12-30-09.pdf

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Attachment E – TCEQ Comments on EPA Dioxin Reanalysis

**Texas Commission on Environmental Quality
Comments Regarding the U.S. Environmental Protection Agency
Draft EPA’s Reanalysis of Key Issues Related to
Dioxin Toxicity and Response to NAS Comments
Notice of Public Comment Period
75 FR 28610, May 21, 2010
Docket ID No. EPA-HQ-ORD-2010-0395**

On May 21, 2010, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register/Vol. 75, No. 98/Friday, May 21, 2010/Notices) of a 90-day public comment period (ending August 19, 2010) for the, “Draft EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments,” hereafter referred to as the draft reanalysis (EPA/600/R-10/038A). EPA will only guarantee that comments submitted by July 7, 2010, will be provided to the Scientific Advisory Board (SAB) in time for their panel meeting for independent external peer review of the draft reanalysis. The draft reanalysis: (1) details EPA’s technical response to the key comments and recommendations included in the 2006 National Academy of Sciences (NAS) report, “Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment,” with a focus on dose-response issues; (2) classifies 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin) as carcinogenic to humans; (3) provides an oral slope factor for TCDD; and (4) provides an oral reference dose (RfD) for TCDD, although EPA has not historically calculated an RfD. The Texas Commission on Environmental Quality (TCEQ) has developed comments on the draft reanalysis to the extent practicable in the time allotted by EPA and provides the following limited comments for EPA consideration.

General Comment:

The assessment of the carcinogenic and non-carcinogenic potential of TCDD has great implications both in a regulatory context and in the public’s perception of risk. Given their important role in the protection of public health, EPA regulatory risk assessors have a duty to perform the most scientifically defensible assessments possible while giving careful and due consideration to comments and recommendations from other regulatory agencies, the public, external experts such as NAS, stakeholders, etc. Although regulatory risk assessors have a penchant for erring on the side of health-protectiveness and conservative defaults, if erring on the side of conservatism significantly overestimates risk or hazard and is not fully justified, then harm to public health may result from diverting public, industry, and government attention and resources away from chemicals that may represent more of a public health risk at environmental levels. Therefore, TCEQ encourages EPA to give full, thoughtful, and careful consideration and evaluation to comments and recommendations from TCEQ, other regulatory agencies, the public, and external experts such as NAS despite the artificial imposition of a December 31, 2010, deadline for release of the final TCDD reassessment.

90-Day Comment Period:

The 90-day comment period is insufficient for regulatory agencies and others to provide thorough and meaningful comments based on an in-depth review and analysis of the draft reanalysis. There is great complexity associated with multiple issues relevant to the assessment of TCDD risk and hazard due to oral exposure. The draft reanalysis alone is 1,850 pages, with the SAB comments relevant to EPA’s draft

reanalysis being another 268 pages, and hundreds of pages of other documents (e.g., EPA draft for NAS review, EPA response to NAS review document) and studies relevant to the assessment of TCDD risk and hazard due to oral exposure. Given the complexity and volume of relevant materials, it is impracticable for EPA to expect detailed specific comments from external experts given the short period allowed for a critical review of the draft reanalysis and procedures employed by EPA. The 90-day comment period only allows a very cursory review of the draft reanalysis at best, leads to a less-than-desirable level of transparency and peer review, and undermines confidence in the process. Consequently, TCEQ is only able to provide preliminary comments based on a cursory review of the draft reanalysis.

If EPA seeks detailed and meaningful public input and technical comments, at a minimum EPA should: (1) extend the comment period at least 90 days past the August 19 deadline to allow stakeholders to perform a more detailed review of the volumes of relevant information and to comment on problematic issues associated with the draft reanalysis; (2) reschedule the SAB panel meeting to 90 days past the original dates of July 13-15; and (3) similarly extend the July 7 deadline for submitting comments for SAB consideration prior to the panel meeting.

Toxicology-Based Comments:

The complexity of the dose-response analyses of dioxin toxicity (cancer and non-cancer) and the potential for significant implications associated with the SFo (1E+06 per mg/kg/day) and RfD (7E-10 mg/kg-day) provided in the draft reanalysis indicate that EPA should allow a longer comment period for stakeholders to prepare more detailed comments. The allotted 90 days to prepare comments (August 19, 2010 deadline): (1) does not provide for an appropriate level of technical peer review for a draft 1,850-page document which represents years of work (e.g., dose-response analyses); (2) undermines confidence in the analyses and cited SFo and RfD values; and (3) calls into question the transparency of the TCDD toxicity factor development process as a thorough scientific review during this time frame is essentially unfeasible. Requiring comments be submitted by July 7, 2010, to be considered by SAB prior to the SAB panel meeting exacerbates the already significantly inadequate review time. Consistent with the inadequate review time allotted by EPA, extremely limited general toxicology-based comments are provided below.

Extrapolation Approach for the Carcinogenic Assessment

EPA has chosen to use a linear, low-dose extrapolation method for cancer effects as opposed to a nonlinear extrapolation method as recommended by NAS. EPA should adopt a nonlinear approach per the NAS committee, who unanimously agreed that the current weight of scientific evidence on the carcinogenicity of TCDD is adequate to justify the use of nonlinear extrapolation methods. TCEQ concurs with the NAS that scientific evidence (e.g., mode of action, tumor dose-response data) is adequate to favor the use of a nonlinear model that would include a threshold response over the use of the default linear assumption. This determination is based on several lines of evidence, including: (1) available data suggest that TCDD (and other dioxins and dioxin-like compounds) are not directly genotoxic, and there is general consensus in the scientific community that nongenotoxic carcinogens exhibit nonlinear dose-response relationships and thresholds (doses below which the expected response would be zero) are likely to be present; (2) there is widespread agreement in the scientific community that all or nearly all the adverse effects of TCDD (and other dioxins and dioxin-like compounds) depend on a receptor-mediated mechanism, acting through a mechanism involving the Ah receptor, and Ah receptor

activation is a phenomenon that would be likely to cause the dose-response relationship to be sublinear at low doses (indeed, EPA has determined in previous evaluations of receptor-mediated carcinogens (e.g., numerous pesticides) that a nonlinear, low-dose model that may accommodate a threshold is appropriate); and (3) there is evidence of nonlinearity in various dose-response relationships for TCDD-induced tumors. In regard to (3) above, evidence of substantial hepatotoxicity and a sublinear dose-response relationship in tumor-bearing female rats suggests that linear low-dose extrapolation is inappropriate. Additionally, for two types of epithelial tumors (keratinizing epithelioma of the lung and squamous cell tumors of the oral mucosal epithelium) the shape of the dose-response relationship suggests that they may be nonlinear. Also, the recent National Toxicology Program bioassay data (NTP 2004) are more consistent with a sublinear response that approaches zero at low doses rather than a linear dose response. Such evidence supports a nonlinear, low-dose extrapolation method as more justified and appropriate than the linear, low-dose extrapolation method used by EPA. However, contrary to the NAS and this evidence, EPA concludes that there is insufficient evidence to support a nonlinear approach. EPA should adopt a nonlinear approach per the NAS recommendation as the weight of scientific evidence supports it.

Additionally, EPA chose to use a 95% upper confidence limit (95%UCL) over the statistical best estimate of the regression coefficient. If EPA elects not to follow the NAS recommendation for a nonlinear approach, TCEQ suggests use of a SFO based on the best estimate of the regression coefficient as opposed to the 95%UCL. Based on Table 5-4 of the draft reanalysis, a SFO of around $5E+05$ per mg/kg/day is preferred over use of the 95%UCL SFO as it is based on the statistical best estimate of the regression coefficient. This human study-based SFO is very similar to and supported by the SFO based on the well-conducted NTP (2006) rat study (Table ES-2), the most comprehensive evaluation of TCDD chronic rodent toxicity to date. Based on a very cursory review of the 1,850-page draft document, it does not appear to address, much less justify, use of a 95%UCL over the statistical best estimate of the regression coefficient.

Intrahuman Uncertainty Factor

EPA should give further consideration to justifying the reduction of the intrahuman uncertainty factor (UF_H) from 3 to 1 as the critical effects observed in the co-principal studies used to derive the RfD were found in sensitive subpopulations (children, neonates). There is historical precedent for EPA using a UF_H of 1 when the RfD is based on data in sensitive subpopulations such as infants and children (e.g., nitrate, nitrite, fluorine/soluble fluoride). Using a UF_H of 3 as in the draft reanalysis results in an RfD that may be interpreted by the public to mean that based on average U.S. dietary intake (ATSDR 1998), which exceeds the draft RfD, TCDD-induced health effects such as increased thyroid stimulating hormone in neonates are likely occurring in the general population on a widespread basis.

Implementation-Based Comments:

Again, EPA must consider providing adequate review time for a critical examination of the bases of the SFO and RfD because these values have significant consequences for issues such as food safety, the federal drinking water maximum contaminant level (MCL) and surface water quality standards, and preliminary remediation goals (PRGs) applicable to dioxin (and other dioxin-like compounds) in soils at Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA/Federal Superfund) and Resource Conservation and Recovery Act (RCRA/Federal Hazardous Waste) corrective

action sites. Consistent with the inadequate review time allotted by EPA, extremely limited general implementation-based comments are provided below.

Food Safety

TCEQ questions the risk assessment utility of an RfD value that is within or below the range of reported average dietary intake. The average intake from meat and eggs alone exceeds the RfD (ATSDR 1998). This draft RfD inevitably would raise public concerns about the safety of the U.S. food supply, especially given that the public frequently interprets the exceedance of a regulatory value as equivalent to an expectation of the occurrence of adverse health effects. A margin of exposure approach appears more appropriate than an RfD to evaluate the potential for non-cancer effects. The SFO provided in the draft reassessment also raises concerns about food safety given that risk from average dietary intake is above the acceptable excess risk range (1E-06 to 1E-04) established by EPA. Analyses such as these, using the RfD and SFO from the draft reanalysis, would imply that the U.S. diet results in TCDD hazard and risk that are considered unsafe and unacceptable from a regulatory perspective. Use of unjustifiably conservative toxicity factors for a chemical (or class of chemicals) may unnecessarily alarm the public and result in at least two negative responses: diluting the message of any future government risk warnings or diverting focus, funding, and resources from chemicals which realistically represent more of a public health hazard.

Surface Soil PRGs

The SFO given in the draft reanalysis (1E+06 per mg/kg/day) is 6.4 times higher than that used for the interim preliminary PRGs (1.56E+05 per mg/kg/day; EPA 2009), so revised cancer-based PRGs could be a factor of 6.4 times lower. The new RfD (7E-10 mg/kg-day) is 30% lower than that used for the interim preliminary PRGs (1E-9 mg/kg-day; EPA 2009), so revised non-cancer-based PRGs could decrease by 30%. Although the interim preliminary PRGs were ultimately based on non-cancer PRGs (EPA 2009), the greater conservativeness of the SFO given in the draft reanalysis may cause cancer-based PRGs to be the critical final PRGs. If protective at the 1E-05 excess risk level (similar to the interim preliminary PRGs in EPA 2009), the residential and commercial/industrial worker surface soil PRGs could be over 150 times lower than the current PRGs (1 ppb for residential; 5 ppb for commercial/industrial (lower end of the range); EPA 1998), with the final residential PRG possibly being within the range of rural background concentrations (EPA 2009). EPA should reconsider finalizing a SFO which may result in setting a final residential PRG within background concentrations because such a PRG would not be feasible from a compliance perspective and could result in costly studies to determine site-specific background concentrations.

In regard to individual excess lifetime cancer risk (IELCR), EPA states on their website (<http://www.epa.gov/oust/rbdlm/sctrlsgw.htm>), “The IELCR represents the incremental (over background) probability of an exposed individual's getting cancer (i.e., a risk occurring in excess of or above and beyond other risks for cancer such as diet, smoking, heredity). Cleanup standards calculated on the basis of excess risk limits correspond to allowable levels *in excess of the background concentrations of the chemicals of concern normally present in the source media*” (emphasis added). Since regulatory agencies are concerned with regulating *excess risk* (i.e., risk over natural background), technically, the risk due to naturally-occurring background soil levels should be excluded from comparisons to the EPA acceptable risk range. In other words, as EPA and other regulatory agencies are concerned with regulating excess

risk over background, background TCDD levels (dioxin/furan TEQ) should be excluded from comparison to the TCDD PRG. Only levels *in excess of background concentrations* should be compared to TCDD PRGs since per EPA, “cleanup standards calculated on the basis of excess risk limits correspond to allowable levels *in excess of the background concentrations.*” Alternatively but based on the same considerations and with the same effect, the applicable soil PRG could be added to a representative background concentration for a site to derive a comparison value that represents a regulatory acceptable level of excess risk (i.e., risk over background). Since EPA is concerned with regulating excess risk over background, EPA should simply acknowledge that no action is necessary when TCDD levels (dioxin/furan TEQ) are within background at a remediation site, even if levels are above the applicable PRG.

Federal Drinking Water MCL and Surface Water Quality Standards

The SFO given in the draft reanalysis also has implications for the federal MCL for TCDD. Using the current SFO (1.56E+05 per mg/kg/day), risk associated with drinking water ingestion at the MCL is at the high end of the risk range deemed acceptable by EPA ($\approx 1E-04$). Use of the draft reanalysis SFO would result in the MCL being associated with a risk ($\approx 9E-04$) significantly higher than the upper end of the EPA acceptable risk range. The new RfD also has significant implications for the MCL. As the relative source contribution factor in the MCL calculation would likely be no greater than 1% (i.e., over 99% of exposure comes primarily from food), for a hazard quotient of 1 the current MCL would likely have to be reduced by over a factor of 100. Derivation of the most scientifically-defensible SFO and RfD values possible is also imperative due to the potentially significant impacts on surface water quality standards.

Recommendation:

Again, if EPA seeks thorough, detailed, and meaningful input and technical comments from the public and external experts on the EPA analyses conducted, at a minimum EPA should: (1) extend the comment period at least 90 days past the August 19 deadline to allow stakeholders to perform a more detailed review of the volumes of relevant information and to comment on problematic issues associated with the draft reanalysis; (2) reschedule the SAB panel meeting to 90 days past the original dates of July 13-15; and (3) similarly extend the July 7 deadline for submitting comments for SAB consideration prior to the panel meeting. If EPA chooses not to provide additional time, EPA should carefully consider the broader consequences of finalizing the draft SFO and RfD values currently proposed, which could result in additional burdensome and costly regulation without meaningful protection of public health.

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