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 mg/L x 2 L/day)/70 kg = 0.0029 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 mg CrVI/L (average) x 2 L/day x 5 years/70 years = 0.0014 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 though 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 unsupportable (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 mutagencity 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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Appendix: Carcinogenic MOA Data Gaps Addressed by the CrVI MOA Research Program

Key Event	Data Gap	Aspect of the MOA Study to Fill Data Gap
1. Saturation of stomach reductive capacity	1. Interspecies differences in the reductive capacity. 2. Dose at which Cr(VI) will not reach the duodenum in mouse	Toxicokinetic data (see next step) will be used to develop and refine species-specific PBPK models for quantifying reduction capacity. PBPK models may be used to extrapolate between species and from higher to lower doses
2. Uptake of Cr(VI) by the intestinal mucosa	1. Measures of Cr absorption into epithelial tissues in rats and mice. 2. Basal and Cr(VI) induced changes in SLCs 3. Differences between intestinal mucosa and that of upper alimentary tract.	Toxicokinetic study 1. measure Cr absorption and accumulation 2. Ex vivo reduction rate and capacity 3. Toxicogenomic analyses 4. Inter-species variability
3. Oxidative stress leading to tissue damage and inflammation	1. Measure of oxidative stress and/or inflammation in the intestines	1. GSH/GSSG ratios in intestinal epithelial tissue and blood 2. Cytokines (22-plex) in intestinal epithelial tissue and blood 3. Gene Expression in intestinal epithelial tissue
4. Intestinal cell proliferation	1. NOEL for intestinal diffuse hyperplasia 2. Mechanistic basis for interspecies differences 3. Driver of proliferation (cytotoxicity, mitogenesis, mutation, etc.)	1. Histopathology in new lower doses 2. Gene expression in intestinal epithelial tissue anchored to pathology 3. Compare all data to determine the cause of proliferation
5. DNA Damage or Epigenetic Changes	1. Measures of DNA damage in target tissue. 2. Are the tumors in the NTP study the result of Cr mediated DNA damage, oxidative DNA damage, proliferative pressure, or some combination?	1. Cr bound to DNA 2. 8-OH-dG 3. Gene expression for changes in DNA repair 4. Genotoxicity in crypts
6. Conversion of DNA damage to mutation	1. Measures of DNA mutations in target tissue 2. Hot spots for Cr(VI) induced mutation? 3. Do mutations occur early or late?	1. In vivo mutation analysis of select codons (e.g., ras codons 12, 13, and 61) or exon sequencing (e.g., p53 exons 5-8).