

**MODIFICATIONS TO THE MAY 30, 2008 ADDENDUM TO THE
SEPTEMBER 28, 2007 “HUMAN HEALTH AND ECOLOGICAL RISK ASSESSMENT”,
ST. REGIS PAPER COMPANY SITE, CASS LAKE, MN**

The U.S. Environmental Protection Agency (U.S. EPA) and its support agency partners reviewed the Addendum to the “Human Health and Ecological Risk Assessment, St. Regis Paper Company Site, Cass Lake, MN” (the Addendum) dated May 30, 2008. (Note: revisions to Section 4.4 were received under separate cover). The Addendum (including revisions to Section 4.4) was prepared by Integral Consulting, Inc., for International Paper (IP). The addendum was reviewed to assess (1) its technical adequacy and (2) whether comments submitted on the previous version of the risk assessment, dated September 28, 2007, had been adequately addressed. Based on its review, U.S. EPA observed that most comments and directives regarding the previously submitted version of the risk assessment had been adequately addressed. Nonetheless, U.S. EPA identified concerns regarding a variety of issues that required modification. U.S. EPA’s modifications appear in the following specific technical review comments. Addendum sections (or portions of sections) modified to address U.S. EPA’s concerns are presented immediately following each comment. New references cited in this modification are listed at the end of this document.

SPECIFIC COMMENTS

Section 4.4.2.3-Carcinogenicity Classification for TCDD

a. p. 4-10, 5th line from bottom - EPA does not agree that “...the designation of TCDD as a human carcinogen is controversial.” IARC, the DHHS, and EPA have all classified TCDD as a known human carcinogen. There may not be consensus on the dose which may be associated, but the understanding that TCDD can cause cancer in people is a consensus. There have also been several recent studies demonstrating human cancer from dioxin exposure.

b. p. 4-11 - discussion of the 2000 SAB (not 2001 panel). There have been several new human cancer studies published since that time. Focusing only on data prior to 2000 is not appropriate. In fact, there is more information from the Seveso cohort clearly showing increase in multiple cancers in comparison of people living in the differentially exposed regions; there is also a clear dose/related increase in breast cancer. In addition, there have been several studies published from the Ranch Hand cohort which clearly show body-burden related increases in several cancers.

c. p. 4-13, top - The NRC only reviewed 3 parts of the complete draft dioxin reassessment - the integrated summary, the dose/response chapter, and the TEF chapter. They did not review all of the supporting chapters.

c. p. 4-13, 3rd paragraph - There is clear understanding that activation of the Ah receptor is necessary for the effects of dioxin. After that required step, there are multiple pathways that can be activated which are cell, tissue, organ, and species specific. There are multiple MOAs, which are different for different endpoints.

REVISED SECTION 4.4.2.3

4.4.2.3 Carcinogenicity Classification for TCDD

In 1985, EPA classified TCDD as a “probable human carcinogen” based on data available in the 1980s and the existing EPA cancer risk assessment guidelines. In its 2000 and 2003 reassessment documents, EPA concluded that TCDD was “best characterized” as “carcinogenic to humans” based on evidence from occupational cohort studies, animal bioassays, and mode of action studies. There is a general consensus among the scientific community that a causal relationship between TCDD exposure and increased incidences of cancer in laboratory animals is adequately supported by existing studies. Similarly, while some uncertainty associated with the dose-response relationship remains, the IARC, the DHHS, and USEPA have all classified TCDD as a known human carcinogen (Howlett et al. 2004; NAS 2006; Pohl et al. 2002; Starr 2003; USEPA 2001c).

There was a lack of consensus among the members of the 2000 SAB panel regarding the strength of weight of evidence for supporting the classification of TCDD as a human carcinogen (USEPA 2001b). The SAB summary of this finding is presented below: HUMAN CARCINOGEN DESIGNATION: EPA has designated criteria for labeling a substance as a human cancer hazard in its draft revised carcinogen risk assessment guidelines (EPA, 1999 and 1996). Criteria for designating human carcinogens differ between these two sets of guidelines and the previous 1986 guidelines. Furthermore, Members of the Panel differed in their level of familiarity with, and their belief in, the applicability of the EPA’s draft cancer guidelines. All of these factors complicated the Panel’s discussion of the human carcinogen designation for dioxin.

“The Panel agrees that causal associations have been established between exposure to TCDD and increased cancer incidence for several types of cancers in both sexes of all species that have been tested. Most Members of the Panel believe that TCDD acts primarily as a cancer promoter rather than as a cancer initiator in these studies. The Panel agrees that the body of such results is sufficient to satisfy the 1999 guideline criterion for compelling evidence of carcinogenicity in laboratory animals for TCDD.

“There is a lack of consensus in the Panel with regard to whether TCDD satisfies EPA’s 1996 draft cancer Guidelines criteria for a human cancer hazard. There is disagreement about the strength of the epidemiological data indicating that dioxin is carcinogenic in humans (i.e. whether statistically significant associations between exposure and cancer could be concluded to be causal), as well as the scientific data demonstrating similar modes of action in humans and laboratory animals.

“Almost half of the Panel’s Members do not support the classification of TCDD as a human carcinogen, citing what they perceived as: (1) the lack of a consistent carcinogenic response (in terms of dose-response) across the various epidemiological studies; (2) the small relative risks observed in each study over a wide range of exposures; (3) the possible impact of confounders; (4) the lack of understanding of the mechanism of action (as is true for most carcinogens); and (5) the fact that the primary increase

demonstrated by EPA is in total number of tumors (a response not heretofore attributed to any chemical carcinogen).

“Other Panel Members do, however, support the classification of TCDD as a human carcinogen. They believe that the results from studies of TCDD-exposed workers are persuasive, and that the variety of studies from researchers in different countries provide limited but convincing evidence of TCDD’s carcinogenicity in humans, particularly for lung cancer and soft tissue sarcomas. Those Members supporting the classification of TCDD as a human carcinogen (just over one-third of the Subcommittee) cite the fact that an international cohort and four industrial populations with highly exposed subcohorts and sufficient numbers in the populations have all shown increased risks of all cancer types associated with TCDD exposure. In two heavily exposed cohorts who had measured body burdens of TCDD, there were modest but significant increases in risk of all cancers with increases in TCDD levels. These Members point out that epidemiological studies can never prove causality and it is impossible in epidemiologic studies to rule out all confounding factors, such as can be done in animal studies. These Members believe that a single factor other than dioxin exposure can not be identified which could explain the epidemiological findings from multiple countries in multiple industrial settings. It is their position that these data (coupled with the animal data) suggest that, at least in highly exposed groups, TCDD acts as a human carcinogen.

“Some Members note that some of the limitations in the epidemiological data of concern to the Panel Members not supportive of the EPA human carcinogen characterization may be explained by the fact that dioxin is a cancer promoter. For cancer promoters the risks might include different cancers across populations depending on the initiating agents and timing of exposures. These Members acknowledged that the observed risks might be low if the population’s exposure to an initiator is low. Improperly controlling for “confounders” that are cancer initiators could mask the true effect of a promoter.

“With regard to determining the similarities in mode of action between the human and animal data, some Members of the Panel found EPA’s arguments about these similarities persuasive, and concluded that TCDD is a multi-species, multi-organ, carcinogen in male and female experimental animals. Approximately half of the Panel Members hold that the key events in the causation of cancer (i.e. initiation, proliferation, and uncontrolled growth) that precede the cancer response in animals have not been observed in humans (*in-vitro* or *in-vivo*). Other Members disagreed, noting that, in any event, none of the versions of EPA’s cancer guidelines requires that the key events in the causation of cancer be observed in humans in order for a chemical to be considered a human carcinogen.”

It is important to realize that all of the quotes presented above are based on data published prior to 2000 -- several new cancer studies have been published since that time. For example, additional data from the Seveso cohort clearly shows increases in multiple cancers in persons with greater TCDD exposure (Consonni et al. 2008, Baccarelli et al. 2008); there is also a clear dose/response related increase in breast cancer (Warner et al. 2002). Also, several studies published from the Ranch Hand cohort clearly show body burden-related increases in several cancers (Michalek and Pavuk 2008; Pavuk, Michalek, and Ketchum 2006; Pavuk et al. 2003). Finally, two studies published since the release of the 2003 DRA provide further evidence of positive exposure-response analyses (increases in cancers with increases in exposure) and support the classification of dioxins as a human carcinogen (Steenland et al. 2004, Crump et al. 2003).

The NRC expert committee that reviewed the 2003 reassessment also expressed concern over EPA’s conclusion that 2,3,7,8-TCDD should be classified as carcinogenic to humans. (Note: the NRC reviewed three portions of the draft dioxin reassessment -- the integrated summary, the dose/response chapter, and the TEF chapter. The NRC did not review all of the supporting chapters). Most notably, the committee as a whole was not convinced that the available data on the human carcinogenicity of TCDD met all of

the classification criteria outlined in EPA's revised cancer risk assessment guidelines (USEPA 2005b). These guidelines state that for a chemical to be classified as carcinogenic to humans there must be strong evidence of an association between human exposure and either cancer or the key precursor events of a chemical's mode of action. Although the committee generally agreed that the epidemiological studies showed a positive association between occupational dioxin exposure and mortality from all cancers, the magnitude of the effect was only modest. In addition, the NRC report criticized EPA for not providing a comprehensive analysis of the full body of epidemiological evidence. Rather, EPA highlighted the positive findings of total cancers in each study and did not address the lack of consistency among specific tumor sites across studies. Although there is a limited amount of information on specific tumor sites among the studies reviewed, the committee concluded that an analysis of specific cancers is warranted (NAS 2006).

The NRC report further indicated that the binding of TCDD with the human Ah receptor may not meet the cancer risk assessment guidelines criteria of being the necessary "key precursor event" for human carcinogenicity. Based on a review of animal studies, the committee found that binding with the receptor is necessary, but not sufficient, to cause cancer in animals. It was noted by the committee that several other substances bind to the Ah receptor without causing cancer (NAS 2006).

The specific mechanisms of action of TCDD are still the subject of ongoing research, and scientific evidence that the mode of action is similar across humans and animals is needed to clarify the carcinogen classification issues for TCDD and other dioxins. Note: understanding is clear that activation of the aromatic hydrocarbon (Ah) receptor is necessary for the effects of dioxin. After that required step, multiple pathways can be activated that are cell-, tissue-, organ-, and species-specific. Furthermore, modes of action (MOA) differ for different endpoints.

Section 4.4.2.4 - Cancer Dose-Response Model for TCDD

a. p. 4-13, first sentence in this section: EPA did not assume a linear approach. It based its decision to use the linear model after analyzing all of the data and finding that while some responses clearly fit threshold models, others were best fit by non-threshold models. The decision for cancer to model using a non-threshold model was based on this fact and the policy that, in the absence of clear proof of a threshold, to use a linear model.

b. p. 4-14, last sentence in first paragraph - TCDD is a complete carcinogen in animal bioassays - this not proof that dioxin is a promoter. In tumor promotion studies (at multiple sites), TCDD does function as a tumor promoter.

c. p. 4-14, 2nd paragraph - The reversibility of TCDD "promotion" has been studied by the NTP using "stop" studies. What they found was that while the total number of tumors decreased, the tumors that persisted were larger. It is, therefore, inaccurate to say that TCDD carcinogenesis is reversible. The issue of "threshold" is one of detectability; what you can measure. There is also less an issue of extrapolation to lower doses - many of the animal studies result in body burdens that are not far above that in some of the human epidemiology studies.

d. p. 4-14, 3rd paragraph - Activation of a receptor is based on mass-action and is therefore not a "threshold" process - detection of this activation may have a threshold. Sigmoidal dose/response curves on a semi-log basis are linear on an arithmetic basis.

e. p. 4-14, 4th paragraph - It is not true that all of the hepatic tumors are associated with hepatotoxicity. This issue was examined by Bob Maronpot of NTP and while some of the tumors were associated with liver toxicity, not all were. Also, there are many tumors other than liver tumors, both in the Kociba study, the recent NTP studies, as well as all of the other studies (18) of TCDD carcinogenicity in rats, mice, hamsters, and fish. It is also inaccurate to state that the EPA analysis was based solely on the Kociba study - in fact, the EPA cancer conclusions and dose/response were largely based on an analysis of the human industrial cohorts. The risk estimated from 3 human data sets was almost identical to the Kociba rat data.

f. p. 4-15, last sentence of 1st paragraph - This should be restated as an opinion, not science.

f. p. 4-15, removal of 2nd and 3rd paragraphs - This version ignores all of the modeling of the human data which was conducted, and also ignores all of the more recent human data.

REVISED SECTION 4.4.2.4

4.4.2.4 Cancer Dose-Response Model for TCDD

In the most recent draft of the dioxin reassessment, EPA selected a nonthreshold linear approach for modeling dioxin dose-response relationships and for calculating the CSF of 1×10^6 (mg/kg-day)⁻¹ (USEPA 2003f). EPA selected the nonthreshold linear model after analyzing all of the data, finding that while some responses clearly fit threshold models, others were best fit by nonthreshold models. The decision to select a nonthreshold linear model for cancer was based on this and EPA's policy to use a linear approach in the absence of clear proof of a threshold.

However, the 2006 NRC report, as well as the 2000 SAB panel members, identifies four lines of evidence indicating that this assumption is inconsistent with what is known about the mode of action of TCDD and other dioxins. First, research shows that TCDD is not directly genotoxic (USEPA 2003f). That is, it does not directly damage genetic material, or DNA, and therefore is not a mutagen that initiates cancer. Instead, TCDD is viewed as a cancer promoter, which while not carcinogenic itself, may act to enhance the effects of other substances known to be carcinogenic (USEPA 2003f). The lack of evidence of cancer-initiating activity by TCDD in animal studies further supports this observation (NAS 2006). To restate, TCDD is judged a complete carcinogen in animal bioassays -- this in itself is not proof that dioxin is a promoter. However, in tumor promotion studies (at multiple sites), TCDD has functioned as a tumor promoter.

Cancer promoters are thought to act by interrupting intercellular communication essential to controlling the behavior of abnormal cells. They are distinct from cancer initiators in that the effects of promoting agents may, in some cases, be reversible when administration to laboratory animals is reduced or discontinued (Klaassen 1996). The dose-response curves of cancer promoters or substances that are not genotoxic are typically nonlinear with an observable threshold and maximal effect levels (Klaassen 1996;

Peterson et al. 1994). As specified in EPA's revised cancer risk assessment guidelines (USEPA 2005b), extrapolation to lower dose levels should be consistent with the current understanding of the mode of action, including those that assume nonlinearity in dose-response relationships. The reversibility of TCDD "promotion" has been studied by the NTP using "stop" studies. The NTP found that, while the total number of tumors decreased, the tumors that persisted were larger. Therefore, it would be inaccurate to say that TCDD carcinogenesis is reversible.

Second, TCDD produces toxic effects by binding with a receptor, called the aromatic hydrocarbon receptor, or Ah receptor. This binding, in addition to ligand-receptor interactions and subsequent molecular events, results in a complex, multi-step process to produce dioxin toxicity (NAS 2006). A fundamental concept in pharmacology is that chemicals that act via a receptor-mediated process produce sublinear responses at low doses. These chemicals yield sigmoidal-shaped log dose-response curves (NAS 2006). In previous evaluations of other receptor-mediated carcinogens, EPA concluded that use of a nonlinear, low-dose model was appropriate for risk assessment. Specifically, EPA considers many pesticides that cause thyroid cancer secondary to effects on thyroid hormone levels as carcinogens with nonlinear behavior (NAS 2006). It should be noted that activation of a receptor is based on mass-action and is therefore not a "threshold" process. Rather, detection of this activation may have a threshold. Sigmoidal dose/response curves on a semi-log basis are linear on an arithmetic basis.

Third, NAS (2006) cites evidence that the rat liver tumors observed by Kociba et al. (1978), the study relied upon by EPA to develop a dioxin dose-response relationship, are secondary to hepatotoxicity caused by TCDD. Studies by NTP (1982; 2004; 2005) also demonstrated that dose-related hepatotoxicity preceded increases in liver tumors in rats exposed to TCDD. Numerous studies have shown that chemical hepatotoxicity leads to increased cell proliferation (NAS 2006). This proliferation, or tumor development, may be secondary to the toxicity rather than directly attributable to the chemical (USEPA 2005b). The cancer risk assessment guidelines (USEPA 2005b) caution against using tumor data for quantitative, low-dose extrapolation "when clear evidence of cytotoxicity is present" and the "mode(s) of action underlying the tumorigenic responses at high doses is not operative at lower doses." These observations and the criteria set forth in USEPA (2005b) calls into question the validity of relying on the liver tumor data from Kociba et al. (1978) for quantitative, low-dose extrapolation and calculation of a CSF for TCDD. However, this conclusion must be considered in light of some contrasting information, as discussed below.

Specifically, NTP's examination of the link between hepatic tumors and hepatotoxicity revealed that while some tumors were associated with liver toxicity, not all were. It should also be noted that other types of tumors were reported in Kociba et al. (1978); the recent NTP studies (Walker et al. 2005, Yoshizawa et al. 2005a, Yoshizawa et al. 2005b, Hailey et al. 2005, Brix et al. 2004, and Nyshka et al. 2004); and other studies of TCDD carcinogenicity in rats and mice (USEPA 1985b, Huff et al. 1991, Zeise et al. 1990, and IARC 1997), hamsters (Rao et al. 1988), and fish (Johnson et al. 1992). Furthermore, EPA's analysis was not based solely on the Kociba study -- in fact, EPA's cancer conclusions and dose/response were largely based on an analysis of the human industrial cohorts (USEPA 2003). The primary point was that the risk estimated from three human data sets was almost identical to the Kociba rat data (Kociba et al. 1978, USEPA 2003f).

Fourth, evidence of the nonlinear threshold relationship between dioxin dose and tumor response has emerged from the most recent bioassays conducted by researchers at the National Toxicology Program (NTP 2004; Walker et al. 2005). Data from NTP (2004) show a consistent sigmoidal shape to the TCDD tumor dose-response curves (NAS 2006). While conducting a dose-additivity study on dioxin and two dioxin-like chemicals, Walker et al. (2005) found that the dose-response shapes for all cancers in animals dosed with TCDD, 2,3,4,7,8- pentachlorodibenzofuran (PeCDF), or PCB 126 were "highly nonlinear." NAS (2006) agreed in its report that the observed data from Walker et al (2005) are consistent with a

sublinear response that approaches zero at low doses; however, because of small sample size and limited statistical power, one also cannot discount a linear response at doses below a 5 percent response level. Based on these results, it is likely that other dioxin-like compounds, individually and as mixtures, exhibit nonlinear dose-response relationships in the low dose region. (Note: this last statement is based on professional judgment.)

In summary, the NAS (2006) review report states that while it is not scientifically possible to completely exclude the assumption of linearity at low doses, the scientific evidence on TCDD “favors the use of a nonlinear model over the default linear assumption to extrapolate below the POD for dioxin-related cancer risk.” The committee “unanimously agreed that the current weight of scientific evidence on the carcinogenicity of dioxin is adequate to justify the use of nonlinear methods to extrapolate below the POD.” As a result, the committee recommended that EPA calculate CSFs using both models and describe their strengths and weaknesses for risk management purposes, specifically acknowledging that a sublinear model will only yield lower risk estimates than a linear model if the background exposures are lower than the POD. The committee advised that using a linear-based CSF as a default assumption for regulating TCDD should be made as part of risk management not risk assessment activities (NAS 2006).

Section 4.4.2.5 - Selection of Data Sets and Points of Departure for Estimating TCDD CSF

a. p. 4-17, last sentence in 3rd paragraph just before starting new 4.4.2.6 - It should be clearly stated that the NRC was using a 200r new cancer RA guidelines to critique when the Agency put out as the draft DRA in 2003 - the years when these things occurred should be in the sentence.

REVISED SECTION 4.4.2.5

4.4.2.5 Selection of Data Sets and Points of Departure for Estimating TCDD CSF

In the 2003 draft reassessment, EPA relied on one POD (the effective dose at the 1 percent response level, or ED₀₁) from data collected for one tumor site and one animal species in a single animal bioassay (Kociba et al. 1978) to calculate its proposed CSF of 1×10^6 (mg/kg-day)⁻¹. EPA also used one dose-response model to generate the ED₀₁. In selecting this approach, EPA chose from a limited number of animal studies and focused on tumor types for which increased incidence with dose was observed. The NRC was critical of this approach in its report. Specifically, the NRC report concluded that “EPA had not adequately justified use of the 1% response level as the POD for the analysis of either the epidemiological or animal bioassay data” and “reliance on one site from one gender of one species, as reported by a single study, does not adequately represent the full range of data available.” In fact, the NRC questioned why EPA chose to rely on one tumor site in animals while considering all tumor types combined when quantitatively evaluating the human epidemiological data.

The NRC determined that use of other animal and human data sets and consideration of all tumor types would yield a substantially wider range of PODs, and thus potency estimates, than those presented in the 2003 reassessment. For example, ED₀₁ values calculated using all the animal bioassay data sets and dose-response model considered by EPA (i.e., data sets from Kociba et al. 1978 and NTP 1982 that suggested tumor incidence increases with dose) range as high as 1,190 ng/kg (whereas the ED₀₁ calculated by EPA is 31.9 ng/kg). Use of an alternate dose-response model, such as the model developed by Portier and Kohn (1996), to analyze the Kociba et al. (1978) data yields a substantially lower ED₀₁ of 2.7 ng/kg (NAS 2006). Similarly, the NRC committee estimated the range of plausible ED₀₁ values, including lower- and upper-bound values, using the human epidemiological data. They found that the range spans at least 1 to 2 orders of magnitude, not only among the three studies used, but also within each study (e.g., ED₀₁ values ranged from 6 to 1,000 ng/kg in just one study) (NAS 2006). The fact that there is a wide range of values possible is indicative of the high degree of uncertainty in both the existing data and in calculation of a CSF.

EPA notes in the reassessment that while the ED₁₀ is generally used to estimate a CSF, if more sensitive data are available, a lower point, such as the ED₀₁ can be used. However, based on the 2005 cancer risk assessment guidelines, the NRC states that a lower response level (i.e., ED₀₁) is “justified only if the estimated dose corresponding to this response is insensitive to the functional form.” The NRC committee concluded that the dose-response functions for the epidemiological data identified by EPA suggest that this criterion is not satisfied (NAS 2006).

Thus, the NRC committee recommended that EPA consider the full range of data to estimate PODs and CSFs, and consider alternate PODs (e.g., ED₀₅ and ED₁₀). The data should include, among others, those from the new NTP animal bioassay studies that have been published since the 2003 reassessment. This recommendation is consistent with the 2005 cancer risk assessment guidelines, which recommend that risk assessors should “present the central estimate and the corresponding upper and lower statistical

bounds (such as confidence limits) to inform decision makers.” The NRC also found that the reassessment did not satisfy other conditions of the cancer risk assessment guidelines, including demonstrating that the POD is insensitive to dose-response functional form (NAS 2006). (Note: it is important to understand that the NAS was using 2005 guidance (USEPA 2005b) in reviewing the DRA published in 2003.)

Section 4.4.2.6 - Consideration of Toxicokinetics in TCFDD Dose Response Assessment

- a. p. 4-17, last sentence - it should be noted that the Carrier et al model was in 1995.
- b. p. 4-18, 2nd to last sentence of first paragraph - the issue is elimination, not metabolism - we have no measure of an effect of age on metabolism; what is seen is a different rate of elimination.
- c. p. 4-18, 3rd paragraph - the non-linearity of elimination is driven by high doses; if you are dealing with background populations, there is little "dose" effect - but what does play a role at background exposures is body adiposity.
- d. p.4-19, last sentence of 1st paragraph - Change the word "critical" to "important" - it is important to consider dose dependency, but may not be critical at background levels.

REVISED SECTION 4.4.2.6

4.4.2.6 Consideration of Toxicokinetics in TCDD Dose Response Assessment

The assumed half-life for dioxin in humans is a key parameter in estimating peak body burdens and hence, exposures in the occupational cohorts relied upon by EPA to generate CSFs (Aylward et al. 2005a; NAS 2006). In the 2003 draft reassessment, the exposure estimates and the dose-response assessment of workers in these cohorts were based on back-calculations of serum lipid TCDD levels over several years assuming fixed first-order elimination rates (USEPA 2003i). Recent analysis of TCDD toxicokinetics, however, demonstrates that TCDD elimination from the human body is both dose-dependent and age-dependent (Aylward et al. 2005a, Emond et al. 2005). These findings call into question the accuracy of the reconstruction of historical exposures in occupational cohorts.

In a recent examination of data from high TCDD exposure cases (patients in Vienna, Austria, and workers in Seveso, Italy), Aylward et al. (2005a) found that the elimination rate of dioxin from humans is dose-dependent and significantly faster at higher exposure levels than previously thought. Using data from the Seveso, Italy, cohort, Aylward et al. (2005a) reconstructed exposure estimates for a subset of the National Institute for Occupational Safety and Health (NIOSH) cohort EPA relied upon to calculate the TCDD CSF. They estimated exposures using a concentration- and age-dependent elimination model (CADM) (Aylward et al. 2005b), modified to account for the apparent differences in elimination processes assumed in the model and those observed in humans.

Depending on the dose metric and summary measure selected, exposure estimates were at least 25 times as high as previous estimates obtained assuming a constant elimination half-life of 7.5 years. Aylward et al. (2005a) found that the elimination rate for TCDD varies with body concentration, with substantially faster elimination at elevated body concentrations than at lower body concentrations. Thus, at peak concentrations, which were assumed to occur during the last year of exposure, elimination of TCDD was highest. In addition, their analyses showed that TCDD half-life was positively correlated with age,

indicating that younger individuals on average eliminate TCDD more rapidly than older individuals. Gender of exposed individuals also substantially influenced the TCDD half-life, with males eliminating TCDD faster than females.

Studies of Emond et al. (2005, 2006) also suggest a dose-dependent elimination rate for TCDD. Emond et al. (2006) developed a physiologically based pharmacokinetic model in the Sprague-Dawley rat that included an inducible elimination rate of TCDD. This model was then extrapolated to human exposure (Emond et al. 2005). Data from a random selection of veterans from the Ranch Hand cohort and data from a human volunteer who was exposed to TCDD were used to optimize the model. Additional data from the Ranch Hand cohort and a clinical report of two women exposed to TCDD were then used to assess the model. The authors state that “this model suggests that previous exposure assessments may have significantly underestimated peak blood concentrations, resulting in potential exposure misclassifications” (Emond et al. 2005).

These results clearly indicate that for human dose estimates back-calculated over long time periods and to elevated body burdens, the assumption of simple first-order elimination kinetics is not valid because of the nonlinear nature of the elimination process (Aylward et al. 2005a). It should be noted that the non-linearity of elimination is driven by high doses; in exposures to background populations, few “dose” effects are evident -- however, body adiposity does play a role. It is likely, therefore, that previous cancer dose-response assessments of the TCDD-exposed occupational cohorts have underestimated exposures, leading to an overestimation of the TCDD CSF presented in EPA's reassessment.

In the reassessment, EPA did compare the impact of using a shorter half-life (4 years vs. the default 7.1 years) on back-estimating occupational exposure and observed that the impact could become “significant if the models predict prolonged periods with half-lives of less than 4 years.” In fact, the NRC committee asserts that the difference in the default vs. shorter half-life assumptions would have increased the estimated ED₀₁ values presented in the reassessment by several fold, with a similar decrease in CSF estimates (NAS 2006). As a result, the NRC committee suggests that EPA quantify the impact of using the shorter half-life for all of the occupational cohorts and consider the analysis by Aylward et al. (2005a).

In a follow-up exposure reconstruction for the TCDD-exposed NIOSH cohort, Aylward et al. (2005b) compared exposure estimates obtained from the concentration- and age- dependent elimination model (CADM) described in Aylward et al. (2005a) with those obtained from first-order models, while varying input parameters. They found that the CADM yielded better model fits to the serum sampling data compared to the first-order models and that dose rates varied by a factor of 50 among different combinations of model type (i.e., first order vs. CADM), parameter inputs, and regression models. When these dose rates were combined with individual time-specific exposure scores¹ to estimate cumulative serum lipid concentrations in the more highly exposed members of the cohort, the CADM yielded estimates that were up to five times greater than those obtained using the first-order models assuming a fixed half-life. The results from Aylward et al. (2005b) demonstrate that incorporating concentration-dependent kinetics is important when estimating the cancer dose-response behavior of TCDD in humans.

More recent analyses of the data from the NIOSH cohort conducted by Cheng et al. (2006) support the Aylward et al. (2005a; 2005b) findings. Using new serum lipid TCDD concentrations derived from the model developed by Aylward et al. (2005b), Cheng et al. (2006) found that the cumulative incremental

¹. Exposure score for each worker is the product of the estimated TCDD concentration (pg/g) in the process materials used in the job, a qualitative contact factor that scores the extent of dermal contact, exposure to airborne particulates in the job, and the estimated time spent actively engaged in the job during the course of a day (Aylward et al. 2005b).

risks of all-cancer mortality in workers up to age 75 are approximately 6- to more than 10-fold lower than those resulting from the previous assessment (Choate et al. 2006), which relied on first-order elimination kinetics and a constant half-life of 8.7 years. Specifically, Cheng et al. (2006) calculated cancer potency estimates for the NIOSH data set ranging from approximately 1×10^4 (mg/kg-day)⁻¹ to 2.4×10^5 (mg/kg-day)⁻¹ compared to the draft reassessment estimate of 1×10^6 (mg/kg-day)⁻¹ using the Steenland et al. (2006) analysis. Because EPA also relied upon first-order elimination kinetics for analyses of the other occupational cohorts, application of the CADM to these data could have similarly significant impacts to the associated CSFs.

In addition, the wide range of dose rates, serum lipid concentrations, and cancer risk estimates generated by Aylward et al. (2005b) and Cheng et al. (2006) strongly suggest that cancer potency estimates should explicitly acknowledge the large degree of inherent uncertainty due to the limitations in the occupational exposure scores, inter-individual variability in elimination and body characteristics, variation in background exposures over time, and uncertainties in dose rates linked to regression-model assumptions (Aylward et al. 2005b).

4.4.2.7 Relative Toxicity of Mixtures of Dioxins, Furans, and Dioxin-like Coplanar PCBs

a. p. 4-20, 3rd paragraph – World Health Organization (WHO) has suggested that the TEFs be re-evaluated every 5 years; EPA knows of no specific plans for this to happen in 2010.

b. p. 4-20, last paragraph- If compounds only have an AhR mediated mechanism, there is nothing but simple additivity. However, if other mechanisms are involved, then non-additive interactions can occur.

c. p. 4-21 - 2nd line - replace "antagonistic" with "non-additive"

d. p. 4-21, 3rd paragraph - end of 1st sentence - change "TCDD" to "dioxins"

e. p. 4-21, 1st paragraph under "History of the TEF approach" - 2nd sentence - While there is the most information for TCDD, there is extensive information for most of the other congeners which dominate the dioxins present in humans - there are extensive data on PeCDD, 2,3,4,7,8-PeCDF, and PCB 126 - and these drive the total TEQ.

f. p. 4-22, 2nd paragraph - The 2005 working group modified, not proposed modification, of the 1998 TEFs.

REVISED SECTION 4.4.2.7

4.4.2.7 Relative Toxicity of Mixtures of Dioxins, Furans, and Dioxin-Like Coplanar PCBs

As described in Section 2.4.1, carcinogenic and noncancer risk estimates for dioxin/furan and coplanar PCB congeners are typically calculated using a toxicity equivalency procedure, in which the relative toxicities of individual congeners are summed to yield TEQs. This procedure involves applying TEFs to the reported concentrations for individual dioxin/furan and coplanar PCB congeners for each medium and calculating the 2,3,7,8-TCDD TEQ for each sample. For inclusion in the TEF concept, a compound must show a structural relationship to the PCDDs and PCDFs; bind to the AhR; elicit AhR-mediated biochemical and toxic responses; and be persistent and accumulate in the food chain (Van den Berg et al. 2006). The TEF approach is used by EPA and international organizations and is widely accepted as a reasonable, scientifically justifiable approach.

Studies generally support the use of the TEF (NAS 2006; Staskal et al. 2006; Van den Berg et al. 2006). Various TEF schemes have been developed, and since the early 1990s, WHO has directed efforts to harmonize these schemes, with periodic updates being made to reflect ongoing research. At the time this toxicity assessment was first submitted to EPA in August 2005, the TEF scheme developed in 1997 and published in 1998 (termed the WHO98 TEFs) was the most current. During -2005, WHO led development of an updated TEF scheme that was published in October 2006 (Van den Berg et al. 2006). At EPA's direction, this risk assessment still uses the WHO98 TEFs, with the 2005 TEFs being addressed in the uncertainty analysis. The 2005 revisions of the TEF values may result in as much as a 25 percent decrease in the total TEO in several data sets depending on the matrix and the exposure sources (Bhavsar et al. 2008, Witsiepe et al. 2007), and our risk estimates may be overestimated to a similar degree. The impact of using 2005 TEFs on two EPCs was evaluated in the Uncertainty Analysis (Section 4.6.1).

Despite the general acceptance of the TEF approach, the approach has inherent uncertainties and limitations that need to be clearly articulated to assess the reliability of TEF-based risk estimates. In recognition of these uncertainties and of extensive ongoing research relevant to assessing the toxicity of these mixtures, WHO has planned for periodic reevaluation of the TEFs (Van den Berg et al. 2006). (Note: while WHO has suggested that the TEFs be re-evaluated every five years, EPA is unaware of any plans for this in 2010.) Some critical sources of uncertainty include compliance with the assumptions of dose additivity and parallel dose response curves, the assumption that relative potency of a chemical is equivalent for all endpoints of concern and exposure scenarios, and the high degree of variability among study results used to derive point-estimate TEFs. Among issues stressed by the 2005 WHO committee was that the TEFs are based on intake rather than on internal doses; and certainly not soil/sediment/air values for which an approach using fate and transport modeling should be developed in the future. Also, the group pointed out the need for development of TEFs for other classes of compounds that meet the criteria of the TEQ approach, especially the brominated dioxins and furans.

For example, *in vitro* data or short-term effects in animals, which may be used to develop a TEF, may not be accurately predictive of toxicity or relative potency of a chemical or complex mixture, which may include non-dioxin-like compounds, in humans (Van den Berg et al. 1998). A key underlying assumption in the TEF approach, is that the toxicities of the congeners included in each are dose-additive. (Note: if compounds have only an AhR mediated mechanism, there is nothing but simple additivity; however, if other mechanisms are involved, non-additive interactions can occur.) However, nonadditive effects, both antagonistic and synergistic, have been shown to occur in animal studies (ATSDR 2004; Safe 1998; Van den Berg et al. 1998; Walker et al. 2005). Safe (1998) found that environmental and food residues of dioxin and dioxin-like compounds often include nondioxin-like PCBs that exhibit non-additive effects for some responses.

Scientists have also noted that the range of TEF values for some congeners is very broad, resulting in a high degree of uncertainty associated with the use of point estimates for TEFs (Staskal et al. 2006; Van den Berg et al. 2006). USEPA (2003f) outlined numerous other underlying assumptions, the most important of which may be the assumption that the relative potency of a chemical is equivalent for all endpoints of concern and exposure scenarios. The interactions of other chemicals, including those that are naturally occurring, are also not considered in TEF schemes.

Given these limitations, the implications of using the TEF method in risk assessment are significant and can result in a high degree of uncertainty in the estimates of TEQs for dioxins. The history of development of the TEF approach and additional explanation of some of the uncertainties associated with this approach are described below.

History of the TEF Approach

The TEF approach for dioxins and dioxin-like compounds was developed to facilitate risk assessment and regulation of complex mixtures of these chemicals. Most of the dose response data for dioxins and furans are for TCDD. Detailed toxicity data to support a dose-response assessment for other congeners and mixtures of congeners are variable and in some cases very limited; however, other data are available that may indicate relative potency among congeners. More specifically, much information is available for TCDD, but extensive information exists for most of the other congeners that dominate the dioxins present in humans -- extensive data exist on PeCDD, 2,3,4,7,8-PeCDF, and PCB 126 -- and these congeners drive the total TEQ. Thus, the TEF approach provides a method for expressing the toxicity of mixtures in terms of TCDD TEQs. After several refinements and expert panel meetings, consensus-based TEF values were established by the WHO during a 1997 reevaluation of the originally proposed TEFs (USEPA 2003f; Van den Berg et al. 1998). This TEF scheme (WHO98 TEF) was formally accepted by several countries and health agencies in the late 1990s as the most plausible method available for assessing risks associated with congener mixtures.

In the TEF scheme, each congener is assigned a toxicity value that describes its potency relative to TCDD. A congener-specific environmental concentration is multiplied by its TEF and summed to produce a TEQ or TCDD TEQ for a particular medium. The benchmark congener TCDD is given a TEF of 1, while the other 28 dioxin-like compounds are assigned order of magnitude values reflecting their estimated toxicities relative to TCDD. Dioxin/furan congeners without chlorine atoms in the 2, 3, 7, and 8 positions and PCB congeners that are not coplanar and do not exhibit dioxin-like toxicity are assigned a TEF of zero (Van den Berg et al. 1998).

While the WHO98 TEF scheme is broadly applied for expressing relative potency, there has been recognition among agencies that refinement of it is an iterative process and that new information should be periodically used to improve upon the TEF values. For this reason, WHO, in conjunction with the International Programme on Chemical Safety (IPCS), has established and regularly reevaluated TEFs through expert consultations for the last 15 years (IPCS 1998). During its assessment in 1997, WHO-IPCS agreed to re-examine the TEF concept every 5 years and update the TEF database as needed (IPCS 1998). Most recently, WHO-IPCS announced a project for reevaluating the method used to derive TEFs, updating the relative potency database, and revising the TEF values (IPCS 1998). An expert panel convened in June 2005 to review all new data and evaluate the WHO98 TEFs. The findings of the expert panel and revised TEFs proposed for use in risk assessment were published in October 2006 (Van den Berg et al. 2006).

The panel modified the TEFs for several dioxins, furans, and PCBs based on a review of the revised relative potency database described below. For the majority of the 14 compounds with WHO98 TEFs,

the panel's modifications resulted in decreased TEF values. Five compounds (OCDD, OCDF, PCB 81, PCB 169, and PCB 167) were selected for increases in the TEFs (Van den Berg et al. 2006). The revised TEFs have not yet been formally adopted by EPA and are therefore discussed in this section and in the uncertainty analysis of the HHRA rather than used to derive risk estimates.

Concurrent with the 2005 reevaluation, the NRC committee reviewing the draft reassessment was charged with examining the TEF methodology as presented in the reassessment. Specifically, the committee was charged with providing scientific judgment on the usefulness of TEFs in the risk assessment of complex mixtures of PCDDs and PCDFs and on the implications of uncertainties associated with using TEFs (NAS 2006). The committee concluded that there are inherent uncertainties and limitations in the TEF methodology that need to be addressed. They also indicated, however, that the current TEF methodology is a reasonable approach and widely accepted for risk assessment purposes.

Two main categories of technical concerns with both the WHO98 and 2005 revised TEF values have been identified within the scientific community. These are concerns with the accuracy and completeness of the database used to derive TEFs and with the high degree of variability among study results used to derive point-estimate TEFs. These concerns are discussed below.

TEF Database Issues

The main impetus for the 2005 WHO-IPCS reevaluation of the TEFs was an audit of the underlying relative potency database originally compiled by the Karolinska Institute in Stockholm and used to establish the WHO98 TEFs. During this audit, Haws et al. (2004) discovered a substantial number of unusable or invalid relative potency (REP) values derived from mammalian studies (Haws et al. did not evaluate bird or fish REPS contained in the database). They identified a number of erroneous entries and incomplete information about specific study elements. In addition, the data for several studies were preliminary at the time WHO derived the 1998 TEFs. Many of the studies have since been published but in several cases the REP values and associated study information were modified from the preliminary release of the results. Finally, REP values for any given congener typically represent a heterogeneous data set and often span several orders of magnitude. Despite this wide range of values, no distributions were developed as part of the database because the original version (i.e., the Karolinska database) was not intentionally designed or annotated in such a way as to allow for assessment of variability or uncertainty. As a result, the WHO98 TEFs are point estimates that may reflect an incomplete, inaccurate, and highly uncertain characterization of relative potency among dioxins.

Based on the audit, Haws et al. (2004) refined the Karolinska database by first reviewing all of the studies cited in the database and updating or correcting specific study elements, and then eliminating or modifying individual REP values based on decision criteria described in their paper. They also added information from relevant studies published after the 1997 WHO-IPCS TEF evaluation and developed unweighted REP distributions. The WHO-IPCS expert panel relied upon this refined database to reevaluate the WHO98 TEFs and propose new TEFs (Van den Berg et al. 2006).

Variability in Point-Estimate TEFs

While refinement of the database was a much needed improvement, Van den Berg et al. (2006) and Haws et al. (2004) indicate that there are still significant gaps in knowledge about mammalian REPs used to revise the TEFs, including large differences in REPs for the same congener due to differences in dosing regimens, endpoints, species, mechanisms, and REP calculation methods. While there are advantages to using point-estimates to derive TEFs, this approach does not account for the variability and the underlying uncertainties in the REP database, and it may reflect a bias in judgment within the expert panel.

As a result, the WHO-IPCS expert panel and other scientists have considered developing a probabilistic approach to determining TEFs (Finley et al. 2003; Haws et al. 2004; Van den Berg et al. 2006). If probabilistic approaches are employed, it is essential that weighting factors be applied to REPs that are from different types of studies in order to place more emphasis on studies that are of better quality and that provide data more relevant to relevant endpoints. (Van den Berg et al. 2006). Haws et al. (2006) and Staskal et al. (2006) have recently developed a weighting scheme and used this scheme to develop weighted distributions for two congeners in an attempt to satisfy this requirement.

Section 4.6.1.1 (p. 4-153), Page 32, Paragraphs 2 and 3. The proposed additional text presents the reasons why eight soil samples collected in Area A were not included quantitatively in the human health risk assessment (HHRA). Three of the samples were collected of stained material in a dirt/gravel roadway (RW-CENTER, -EAST, and -WEST). The text states that “people will not be exposed through direct contact on a chronic basis to roadway materials” and therefore, it is not reasonable to apply the HHRA exposure assumptions to these samples. This statement can be misinterpreted.

It is not unreasonable to assume that people may walk along roadways in their neighborhood on a regular (chronic) basis and may be exposed through direct contact as a result. However, such exposure is not likely to be as extensive as assumed for residential receptors. As a result, it is acknowledged that the HHRA residential receptor exposure assumptions are not appropriate for use in evaluating potential roadway exposures. Therefore, the proposed text should be revised to acknowledge the potential for chronic exposure to roadway materials and discuss qualitatively the risks posed by such exposure as compared to residential risks.

REVISED SECTION 4.6.1.1

On p. 4-153 of the addendum, the following new paragraphs are added after paragraph two (end of Section 4.6.1.1):

EPA expressed concern about eight soil samples collected in Area A that were excluded from the HHRA. Three samples were collected of stained material in a roadway (RW-CENTER, -EAST, and -WEST). People may be exposed through direct contact on a chronic basis to roadway materials (for example, as the result of regular walking or bike riding along roadways). However, such exposure is not likely to be as extensive as assumed for residential receptors. Therefore, it would not be appropriate to apply the residential exposure assumptions of the HHRA to these samples. Furthermore, based on field descriptions of the samples indicating that RW-CENTER had to be “chipped out with a shovel” while RW-EAST and RW-WEST were “semiconsolidated, but could be broken up by hand” (Fetter 2004, pers.comm.), it is unlikely that people would be exposed to these materials through inhalation of fugitive dust or that these materials could serve as a source of recontamination through windblown dust. The roadway materials could serve as a source of recontamination to nearby residential properties via leaching or erosion into surface runoff. However, these are considered to be minor potential pathway because these processes would substantially dilute the concentrations of COPCs in the roadway samples.

The TEQdf concentrations in the roadway samples range from 1.81×10^{-5} to 1.64×10^{-3} mg/kg (EAST and WEST, respectively). The CENTER and EAST TEQ results were flagged JEMPC, indicating unreliable data quality. In comparison, the TEQdf EPCs for former operational areas range from 7.21×10^{-4} to 2.57×10^{-3} mg/kg (International Paper and BNSF, respectively). TEQdf concentrations in the roadway samples are within or below the EPC concentrations in the former operational areas. BaPE concentrations in the roadway samples are 0.0844, 0.0260, and 565 mg/kg (WEST, EAST, and CENTER, respectively). In comparison, the BaPE EPCs for former operational areas range from 0.617 to 2.11 mg/kg (International Paper and BNSF, respectively). The WEST and EAST roadway concentrations fall well below the EPC concentrations in the former operational areas, but the CENTER roadway concentration is much higher. Due to the consolidated nature of the CENTER roadway sample, it is not considered a significant potential source of BaPE to nearby residential locations through surface runoff. Similarly, because the CENTER roadway sample is consolidated, the magnitude of any direct exposure to this sample is expected to be less than would be associated with exposure to soil from the adjacent former operational areas. In conclusion, exclusion of the three roadway samples from potential industrial and residential exposure scenarios is expected to contribute only limited uncertainty because of (1) reduced exposure potential as compared to adjacent industrial and residential properties (2) and generally lower chemical concentrations in the roadway samples as compared to the adjacent industrial and residential properties.

A sample of the topsoil (station ID “topsoil” from event “2004 RA”) that was used to fill selected locations on the driveway of the Allen property in 2004 was excluded from the HHRA due to lack of information regarding the areal extent of coverage related to the sample. Instead, the topsoil concentrations used to represent the 17 properties that participated in the IRM were applied to the Allen property. Concentrations of TEQdf and BaPE in the excluded sample (2.45×10^{-7} and 0.0056 mg/kg, respectively) are lower than the topsoil concentrations used in the HHRA (9.94×10^{-7} and 0.0096 mg/kg, respectively), so this was a health-protective decision.

Sample RES-16, which was collected in 2001, was excluded because the property was resampled in 2003 and is represented in the HHRA by samples RES-16A and RES-16B. Concentrations of TEQdf are 4.85×10^{-4} , 2.87×10^{-4} , and 4.82×10^{-5} mg/kg for RES-16, RES-16A, and RES-16B, respectively. RES-16 was analyzed for carcinogenic PAHs while RES-16A and RES-16B were not. The concentration of BaPE in RES-16 is 0.14 mg/kg. The total RME cancer risk for a tribal adult resident with a garden associated with sample RES-16, using assumptions consistent with the HHRA, is 5×10^{-5} . In comparison, the total RME cancer risks reported in the HHRA for RES-16A and RES-16B are 5×10^{-5} and 8×10^{-6} , respectively. The cancer risk associated with the excluded sample is consistent with the risks reported in the HHRA. Exclusion of the sample did not affect risk estimates.

Sample D20-21 on CFP property was excluded from the EPC calculation because it is covered by a geotextile membrane and four inches of gravel. Because the CFP data set had only seven samples, the maximum concentration of 0.0012 mg/kg (E11-13) was used. The concentration of TEQdf in D20-21 is 0.0016 mg/kg, which would have been the maximum concentration in the data set if it had been included. If the EPC for TEQdf on the CFP property were increased to 0.0016 mg/kg, the cancer risk for the worker scenario would be 4×10^{-5} rather than 3×10^{-5} as reported in the HHRA.

Section 4.6.1.2 (p.4-154), Page 34, Paragraphs 1 and 2. The proposed additional text discusses the potential for exposure (and related risks and hazards) through consumption of fish eggs. The text indicates that the Leech Lake Division of Resource Management, referred to as the “Tribal Food Safety

Initiative,” “recommends limiting consumption of fish eggs and livers to ceremonial use only.” As a result, receptors are assumed to consume fish eggs only in small amounts during the spring season.

The “Tribal Food Safety Initiative” presumably recommended a limit on fish egg consumption at least in part because of actual or perceived chemical contamination found in fish eggs that may be consumed by tribal members. But to thus assume reduced intake will occur and state that subsequent consumption of fish eggs is expected only in small amounts is inappropriate. The risk assessment should evaluate potential exposure to fish eggs at their normal, unrestricted rate as part of a traditional tribal lifeways scenario. The proposed additional text should be revised accordingly.

REVISED SECTION 4.6.1.2

On p. 4-154 of the addendum, the following new paragraphs are added at the bottom of the page:

To evaluate the potential impact of the dust contact pathway on total risk results, cancer risks for tribal adults were calculated assuming dermal contact for a combined soil/dust scenario for 350 days per year under the current scenario (post-IRM, no garden). The soil adherence factor was adjusted to account for different dermal loading rates between soil and house dust. The soil adherence factors used in the HHRA were assumed to occur 83 days per year for adults and 150 days per year for children, consistent with the soil exposure frequencies assumed in the HHRA. Dust adherence factors for children were based on the weighted soil adherence factors for “indoor children” in Exhibit 3-3 of USEPA’s (2004i) dermal exposure guidance: 0.01 and 0.06 mg/cm² for the CTE and RME cases, respectively. These values were assumed to occur for the days of the year not spent outdoors (200 days). The weighted annual average adherence factors including both soil and dust for children were 0.02 and 0.12 mg/cm² for the CTE and RME cases, respectively, which are 60 percent of the original soil-only adherence factors (0.04 and 0.2 mg/cm², respectively). Because indoor adherence data are not available for adults, the weighted annual average adherence factors including both soil and dust for adults were assumed also be to 60 percent of the soil-only adherence factors, or 0.006 and 0.04 mg/cm² for the CTE and RME cases, respectively. Cancer risks including dermal contact with house dust at most locations were 7 percent higher than those excluding dermal contact with house dust (range 2–12 percent). At the maximum risk location (RES-16A), the total cancer risk including dermal contact with house dust was 4×10^{-5} , which is the same as the result reported without dermal contact with indoor dust (Appendix D4). This evaluation indicates that while dermal contact with indoor dust probably is a significant exposure pathway, including it in the evaluation is unlikely to alter decision making at the Site. Data supporting the exposure assumptions for contact with indoor dust are lacking, which imparts a higher level of uncertainty than for dermal contact with outdoor soil.

Consumption of fish eggs is a reported practice in the local community. Applicable fish egg and fish liver ingestion rates, however, were not found in the literature. They are expected to be lower than finfish consumption rates. A recent effort on the part of the Leech Lake Division of Resource Management, the Tribal Food Safety Initiative, recommends limiting consumption of fish eggs and livers to ceremonial use only (Persell 2008). This recommendation is due in large part to actual or perceived chemical contamination in fish eggs and livers that may be consumed by tribal members. While how closely these guidelines are followed is unclear, fish egg consumption (even at levels prior to the recommendation) is expected to be limited primarily to the spring spawning season, and potentially constitutes a bolus dosing

situation. Also, on a chronic basis, most receptors are believed to consume significantly fewer eggs than fish fillets.

Some chemicals are more highly concentrated in fish eggs than in fillet tissue, though this is dependent on both the fish species and the chemical in question. As discussed in Section 4.3.2.1, fish egg data were collected from Cass Lake and Pike Bay in 2004. The ratios of mean concentrations of TEQp (WHO98 ND1/2) in eggs to mean concentrations in fillet tissue were 3 for all species combined and 2 for whitefish alone. The ratios of mean concentrations for TEQdf (WHO98 ND1/2) were also 3 for all species combined and 2 for whitefish alone. Assuming limited and seasonal consumption of fish eggs in the diet, it appears that the inclusion of fish eggs would have little impact on the risks associated with overall annual fish tissue consumption. However, note that the risk assessment quantitatively evaluated only chronic exposure to fish fillets. Potential exposures and risks associated with bolus dosing were not evaluated in the risk assessment. The absence of bolus dose results represents a data gap and contributes a moderate amount of uncertainty to the risk assessment results. Again, exposure information including fish egg and liver ingestion rates was not found in the literature and was not provided by the Band. Furthermore, toxicity factors specific or applicable to a bolus dosing situation are not among the toxicity factors recommended by EPA for use in preparing Superfund risk assessments (USEPA 2003h).

Section 4.6.2.5 (p. 4-164), Page 35, Paragraph 4. The explanation provided for decreasing the dermal absorption factor for all chemicals by a factor of 10 in the uncertainty discussion is not compelling. Based on the limited discussion, a factor of 2, 5, or something else could just as easily have been selected. Section 4.6.2.5 should be revised to eliminate identifying a specific lower dermal absorption factor and simply report that the dermal absorption may be lower than was assumed, but that the degree of overestimation cannot be specified.

REVISED SECTION 4.6.2.5

On p. 4-164 of the addendum, the first sentence of paragraph three is revised as follows:

Decreasing the dermal absorption factor for all chemicals by a factor of 10, chosen based on professional judgment as an estimate of the general degree of conservatism for dermal absorption factors, reduces risk estimates for the dermal absorption pathway to 0.1 times the original risk estimate for this pathway (Table D5-1). Note that the selection of a factor of 10 (as opposed to factors of 5, 20, or something else) is associated with at least a moderate amount of uncertainty. It would be more accurate to state that exposures, risks, and hazards associated with the dermal absorption pathway may be lower than was assumed, but that the degree of any overestimation cannot be specified.

Section 5.1.1.3 (p. 5-11), Page 35, Paragraph 6. Concerning the sediment screening value for dioxin, the second sentence of the replacement text (beginning with “Therefore, the”) adds no value to the document, so it should not be added to the text.

Revision

The replacement paragraph identified in the comment has been revised as follows:

The dioxin screening value used in Table 5-4 was derived by the CCME using TEFs for fish, which are more relevant to benthic invertebrates than TEFs for mammals and birds.

Section 5.3.3.1, (p. 5-46), Page 37, Last Paragraph. Specific comment 7 on the Ecological Risk Assessment (ERA) required that polynuclear aromatic hydrocarbons (PAH) concentrations in fish tissue for the Fox Creek exposure area be estimated based on PAH concentrations in Fox Creek sediment. The additional uncertainty analysis for Section 5.5.2.5 on pages 48 and 49 of the addendum does not fulfill this requirement, and the text on those pages should be revised in accordance with the original comment.

Revision

The following sentence was added after the first sentence in the last paragraph on page 48 of the Addendum:

In addition to these factors, because fish readily metabolize PAHs, estimation of fish tissue concentrations based on sediment concentrations is highly uncertain, and for this reason, was not attempted.

Section 5.3.6.2, (p. 5-52), Page 38, Paragraphs 1 and 2. These paragraphs were prepared in response to ERA specific comment 9. The text at the end of the first paragraph does not explain why a tenfold difference between tissue concentrations was selected as a threshold. Please provide a justification for this factor of 10. The third to last sentence in the second paragraph refers to “analytes other than those listed above.” However, the identities of these analytes are not clear. The text should be revised to identify the specific analytes.

Revisions

The following sentence was added after the last sentence in the first paragraph on Page 38 of the Addendum:

The tenfold difference was selected to ensure that that uncertainty analysis sufficiently bracketed the differences in receptor HQs stemming from the different data sets.

The third to last sentence in the second paragraph was revised as follows:

Therefore, because the *Corbicula* and mussels data set was used to represent invertebrates in the diet of raccoon, mink, and kingfisher (i.e., all aquatic omnivorous receptors except mallard), the use of *Corbicula* and mussels to represent the invertebrate tissue was conservative for these receptors for all analytes except lead and zinc in Fox Creek and antimony, dioxins/furans, LPAH, and HPAH in the Channel.

Section 5.3.7.2, (p. 5-57), Pages 38 and 39. The additional text offered to address ERA specific comments 13 (concerning the diet of the raccoon) and 14 (concerning the diet of the muskrat) does not

suffice. We understand the strategy of using a suite of surrogate receptors in an ERA, but it still remains unclear how the (diets of the) raccoon and muskrat do not overlook an opportunistic, non-piscivorous consumer (like the raccoon) and a mid-level consumer that eats invertebrates during a portion of the year (like the muskrat)—a scenario common to aquatic ecosystems in this climate. The text for each receptor could be revised to identify the actual receptors for which the diets are representative.

Revision

The following language was inserted after the third sentence in the replacement paragraph that spans Pages 38 and 39 of the Addendum:

Because the species have high exposure potentials and different diets were evaluated, the selected scenarios evaluated account for differences in exposures due to different feeding strategies and diets that vary seasonally.

Section 5.3.7.2, (Pages 5-53 through 5-59), Pages 40 and 41. The revised text regarding ecological exposure areas for the various receptors explains how the area values in Table 5-22 were derived, but still does not describe how these area values were used in the exposure assessment, as requested in ERA specific comment 10.

Revision

The following text was added to the end of the first paragraph in Section 5.3.2 of the risk assessment report:

Exposure areas were used to calculate COPEC doses for each wildlife species. The dose equation is presented in Section 5.3.7.1.

Section 5.4.3.2 (Page 5-67), Page 43, Second Paragraph. Page 43, second paragraph: The rationale for not selecting lower CTR values available in the CTR database needs further explanation in relation to the concept of independence from exposure concentration and the effect on the conclusions if the lower available CTRs had been used. This uncertainty is particularly germane to mercury.

Revision

The following text was added to the second paragraph on Page 43 of the Addendum:

The fish tissue concentrations listed in Table 5-53 are much lower than selected tissue TRVs, indicating that concentrations of COPECs in fish tissue will not adversely affect fish. Regarding mercury, the Jarvinen and Ankley database included a study exposing rainbow trout for 34 days to 6.4 ug/L mercuric chloride, resulting in a whole body concentration of 0.90 mg/kg associated with significant mortality (LOAEC) and a whole body NOAEC equal to 0.27 mg/kg. One walleye sample presented a whole body mercury concentration that exceeded this NOAEC but was less than the LOAEC. However, several other

studies in the database, including one that evaluated a 60-day exposure period, presented LOAEC and NOAEC values substantially higher. In addition, surface water data collected from the site showed mercury concentrations substantially less than 6.4 ug/L. This line of evidence indicates minimal potential for mercury to accumulate to harmful levels in fish at the Site.

Section 5.4.2.2, (Tables 5-30 through 5-32), Page 50, Paragraph 2. The text indicates that the total organic carbon (TOC) content of laboratory control sediment was estimated at approximately 4 percent. However, the basis for the estimate is not presented.

Revision

The following text is added to the end of the footnote provided on Page 50 of the Addendum:

“ ... based on historical data collected from the sediment when it was being evaluated for use as laboratory control sediment.”

Section 5.5.2.1, (p. 5-96), Pages 44 and 45. The response includes three paragraphs of text that will be added to Section 5.5.2.1 to address ERA comment 25 regarding the omission of the amphipod growth endpoint. The text in paragraph 3 on page 45 states that a 28-day exposure duration is required in order for amphipod growth to be a statistically sensitive endpoint. For this reason, the 28-day amphipod survival and growth test shall be performed to address the uncertainty associated with this data gap and support decision-making regarding the Fox Creek exposure area. Sediment samples from the same stations and depths evaluated in the ERA shall be tested. Concentrations of COPECs evaluated in the ERA shall also be determined for these samples. The following parameters shall also be evaluated for these samples: (1) organic carbon content, (2) pH, and (3) acid volatile sulfides. Prior to sampling, a brief QAPP amendment will be required, for EPA approval, which includes any supplemental SOPs and information supporting the suitability of the diet that will be used in the 28-day test.

Revision

The following new paragraph was added after the third paragraph on Page 45 of the Addendum.

To address this data gap, the 28-day survival and growth test (ASTM Method E-1706) with the amphipod, *Hyallolella azteca*, will be performed on Fox Creek sediments -- collected from the same locations evaluated using the midge bioassay. These samples will also be tested for AVS/SEM, pH, TOC, grain size, and all COPECs except dioxins/furans, PCBs, and pesticides. Prior to sampling, a QAPP amendment and work plan will be submitted for EPA approval.

Section 5.5.2.1 (Page 5-96), Page 45, First and Second Paragraphs. The last sentence of the first paragraph exhibits faulty logic. Because amphipods are not sediment deposit feeders, nutritional quality

of the sediments should not affect their growth, so if similar results to those for *C. tentans* were seen, it would suggest some factor other than nutritional quality of sediments as a cause. Please revise this text accordingly. Also, the second paragraph states that it is not appropriate to speculate about what an amphipod growth test would have shown. We agree, and did not ask that any speculation of this nature be included. Therefore the text should be revised to delete the language regarding speculation about the missing amphipod test results.

Revisions

The last two sentences of the first paragraph on Page 45 should be disregarded.

The second paragraph on Page 46 should be disregarded.

Section 5.5.2.1 (Page 5-98), Page 46, First Paragraph. The evidence does not support the statement in the first sentence, “Although growth may have been impaired in *C. tentans*, this was likely the result of the natural condition of the sediment”. Growth was impaired in *C. tentans*, and the impairment may have resulted from some natural condition of the sediment, or from contaminants, or both. Please revise the text accordingly. Also please include the specific observations that suggest a robust, highly functional wetland community in Fox Creek.

Revision

The first sentence in the first paragraph on Page 46 is revised as follows:

Impairment of *C. tentans* growth may have been caused by contaminants, naturally occurring conditions, or both.

Section 5.5.2.3, (p. 5-104), Page 47, Paragraph 1. The text states that copper critical tissue residue (CTR) in fish from reference areas were exceeded. However, only fish from Ball Club Lake had tissue concentrations in excess of the CTR. The text should be revised.

Revision

The first sentence in the first full paragraph on Page 47 of the Addendum was revised as follows:

The uncertainties associated with the use of whole body CTRs for metals (USEPA 2007d) as a way of predicting toxic effects on fish, suggests that the exceedance of copper in whole fish from the Site, as seen in the fish from Ball Club Lake, is not a reliable indicator of risk to fish.

Section 5.5.2.5 (Page 107), Pages 47 and 48. The revised text does not address the main point of ERA specific comment 8, which is that only the sucker data (and no other species data) were used for exposure point calculations. Using the maximum sucker concentration does not evaluate the uncertainty associated with using only sucker data, unless suckers had the highest concentrations among fish species for all COCs. If this is the case, then state it in the text. Otherwise, maximum concentrations that occur in any fish species need to be evaluated to address the uncertainty.

Revision

The following text was added to the end of the paragraph at the top of Page 48 in the Addendum:

In addition, to determine the impact of assuming that piscivorous wildlife ingest fish with the highest COPEC concentrations, regardless of whether the species is actually ingested, whole body COPEC concentrations of dioxins/furans and HPAHs (COPECs for both Fox Creek and the offshore ecosystem) in suckers used in the Fox Creek exposure assessment were compared to whole body COPEC concentrations determined for other fish species (walleye and whitefish); the concentrations in walleye exceed those in whitefish. Dioxin/furan and HPAH concentrations in walleye were slightly more than twice the concentrations in suckers. The increased exposure point concentrations increased hazard quotients for piscivorous receptors no more than 0.1.

Appendices A, B, and C. These three appendices present comparisons between background and site chemical concentrations in soil and sediment for the HHRA and the ERA (Appendixes A and B, respectively), and for fish tissue (Appendix C). The footnotes in all tables (i.e., combined Tables A-3, A-4, and A-5; B-5, B-6, and B-7; and C-9, C-10, and C-11) that describe interpretation of the quantile test state that a result is significant if $K_o = K_c$. This should be changed to $K_o \geq K_c$.

REVISED TABLES A-3, A-4, A-5, B-5, B-6, B-7, C-9, C-10, AND C-11

The footnotes in each of these tables that describe the interpretation of the quantile test should be read as indicating that a result is significant if $K_o \geq K_c$.

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