

**Comments on:**

**EPA's Reanalysis of Key Issues Related  
to Dioxin Toxicity and Response to NAS  
Comments (External Review Draft)**

**May 21, 2010**

September 2010

**ARCADIS**

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Draft)**

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September 2010

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Comment 33: EPA did not follow its own policy by not preparing a cost benefit analysis of the consequences of implementing the proposed OSF and RfD. 68

Comment 34: The document proposing an OSF and a RfD does not adhere to the IQA and EPA’s Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the EPA (2002a), because it fails to present any information that demonstrates that dioxin in any environmental media presents a *de minimis* risk to human health. 69

Comment 35: EPA did not adhere to Executive Order 12866 in the Draft Interim PRG document. 69

Comment 36: The Draft Interim PRG document does not adhere to the IQA and EPA’s Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the EPA (2002a), because it fails to quantify the impacts of the proposed OSF and RfD on population risks. 70

Comment 37: EPA’s proposed OSF and RfD were not developed in accordance with EPA’s *Science Plan for Activities Related to Dioxins in the Environment* because they do not provide an “analysis of relevant new key studies.” 71

Comment 38: *EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* did not perform any evaluation of the implications of the proposed actions to determine if the actions will actually produce a net reduction in risk to human health. 72

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## INTRODUCTION

On May 21, 2010, the U.S. Environmental Protection Agency (EPA) issued a 1,850-page document entitled *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (External Review Draft)* (EPA, 2010a). This report was prepared in response to the National Academy of Sciences (NAS) expert review and comments on the EPA (2003) NAS Review Draft entitled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*.

ARCADIS has reviewed the EPA's document and has concluded that EPA has not adequately addressed the criticisms and shortcomings of EPA's previous work summarized by the NAS in their 2006 report. Specifically, EPA has ignored NAS' basic and critical criticism that dioxin's mode of action is clearly non-linear, and EPA should abandon its overall approach for dioxin. Instead, EPA has moved forward with its approach that is out of sync with scientists and regulators in all other countries of the world and inconsistent with their own cancer risk assessment guidelines published in 2005. Specifically, the following text from the report's abstract summarizes EPA's current proposal:

"The draft report develops an oral reference dose (RfD) of  $7 \times 10^{-10}$  mg/kg-day based on two epidemiologic studies that associated TCDD exposures with decreased sperm concentration and sperm motility in men who were exposed during childhood (Mocarelli et al., 2008, 199595) and increased thyroid-stimulating hormone levels in newborn infants (Baccarelli et al., 2008, 197059). EPA also classifies TCDD as carcinogenic to humans, based on numerous lines of evidence, including primarily: multiple occupationally- and accidentally-exposed epidemiologic cohorts showing an association between TCDD exposure and certain cancers or increased mortality from all cancers and extensive evidence of carcinogenicity at multiple tumor sites in both sexes of multiple species of experimental animals. Based on a cancer mortality analysis of an occupational cohort (Cheng et al., 2006, 523122), EPA also develops an Oral Cancer Slope Factor of  $1 \times 10^6$  per (mg/kg-day) when the target risk range is  $10^{-5}$  to  $10^{-7}$ . While this draft report provides limited sensitivity analyses of several steps in the cancer and noncancer dose-response assessment, it concludes that a comprehensive uncertainty analysis is infeasible at this time."

In summary, EPA proposes to rely on human epidemiology studies that do not adequately define a causal role of dioxin exposures on reported adverse effects, raise the Oral Cancer Slope Factor (OSF) by a factor of 6.4, and issue a RfD that is lower than the Agency for Toxic Substances and Disease Registry's (ATSDR's)



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Minimum Risk Level that served as the basis for the recently proposed Interim Preliminary Remediation Goal (PRG).

These proposed actions will have significant consequences for all companies and government agencies who have dioxin/furan or polychlorinated biphenyl (PCB) liabilities in any environmental media.

ARCADIS U.S., Inc. (ARCADIS) presents these comments on *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (External Review Draft)* (EPA 2010a) for EPA's consideration on behalf of Beazer East Inc. and three confidential clients. The comments are presented in three sections, as noted below.

- General Technical Comments on EPA's Dose-Response Assessment
- Detailed Technical Comments on the Basis of the Proposed Oral Cancer Slope Factor and the Proposed Reference Dose
- Science Policy Comments

**GENERAL TECHNICAL COMMENTS**

**Comment 1: EPA's Oral Cancer Slope Factor and RfD for TCDD are scientifically flawed and are not based on the "best available science" because they focus on TCDD alone and do not consider the toxicological effects of other dioxin-like compounds.**

EPA (2010a) has focused its dose response assessment on 2,3,7,8-TCDD alone. By their own scientific policies, however, risk assessment of dioxin sites must use the Agency's Toxic Equivalency Factors (TEFs) to calculate a total TCDD Toxic Equivalents concentration (TCDD-TEQ) for all dioxin-like compounds with EPA sanctioned TEFs and treat them as if they have the same toxicity as does TCDD. If total TCDD-TEQ is posing risk to people from exposure to TCDD plus other dioxin-like compounds with TEFs, then EPA must logically base its dose-response assessments on total TCDD-TEQ from both animal and human studies. In animal studies that employ doses of just TCDD, the total administered dose of TCDD-TEQ may be presumed to equal the administered dose of TCDD alone, unless there is contamination of the animals' water, food, air and bedding material. However in human epidemiological studies, people are exposed to all dioxin-like compounds regardless of the sources of their exposures. No worker and no member of the general population is exposed to just TCDD.

It has been widely stated that certain workers are or were exposed to "predominantly TCDD" and that people living in Seveso, Italy in 1976 and thereafter were exposed to "predominantly TCDD." It may, indeed, be true that certain populations were exposed to a total TCDD-TEQ for which the single highest contributing compound was TCDD. This does not change the basic fact that the total TCDD-TEQ exposure was in all cases much greater than the exposure to TCDD alone. The following presents a few citations from the literature that clearly demonstrate that the contribution of other dioxin-like compounds cannot be ignored when performing dose-response assessments for dioxin and dioxin-like compounds. This is a basic logical issue and EPA's focus entirely on TCDD alone shows conclusively that EPA has not used the "best available science" when preparing the 2010 document under review.

Pesatori et al. (2009) measured the concentrations of TCDD, 2,3,7,8-substituted PCDDs, 2,3,7,8-substituted PCDFs and four coplanar PCBs in the serum of 58 subjects who lived in zone A or B surrounding the Seveso explosion in samples collected in 1993-1994.

**TABLE 1**  
**TCDD-TEQ DATA FROM PESATORI ET AL. (2009)**

<b>Zone</b>	<b>Median Serum TCDD (ppt)</b>	<b>Median Serum TCDD-TEQ (ppt)</b>	<b>Fraction of TCDD-TEQ Caused by Other Congeners Than TCDD</b>
A (n=7)	73.3	94.0	22%
B (n=51)	12.4	43.2	71%

In the most highly contaminated zone around the Seveso incident, TCDD-TEQ was dominated by TCDD, but other dioxin-like compounds were present and significant. In the less contaminated zone, other dioxin-like compounds contributed 71% of the total TCDD-TEQ, so their presence cannot be ignored when investigating the health outcomes of people living in the area.

Warner et al. (2005) measured the PCDD, PCDF, and PCB levels in serum of 78 subjects living in Seveso, Italy in 1998-1999. 66 lived in areas other than zones A, B, or R surrounding the 1976 explosion. One lived in zone A. Two lived in zone B, and four lived in zone R. The remaining people lived outside the A,B, or R zones. According to Warner et al. (2005): "The TCDD levels of the seven women from the exposed areas (median = 4.3 ppt, range=<2.3–18.9 ppt) were significantly higher than the 66 women from the nonexposed zone (median = 1.5 ppt, range: <1.5–18.0 ppt) (P=0.002). Total TEQ levels, however, were not significantly different (Zones A, B, R (mean (range) = 34.8 ppt (10.9–63.5)) versus Zone non-ABR (n=66, mean (range) = 24.2 ppt (0.3–88.3)), P=0.11)." So, for the people living in the zones contaminated by the Seveso explosion, the median TCDD-TEQ serum concentration in 1998-1999 was 8 times higher than the median TCDD concentration.

In 2000-2001, Weiss et al. (2003) measured the PCDD, PCDF, and PCB levels in mother's milk of twelve women who lived all their lives in zones A, B, or R surrounding the Seveso, Italy explosion. All of the mothers were born between 1969 and 1976.

**TABLE 2  
TCDD-TEQ DATA FROM WEISS ET AL. (2003)**

<b>TCDD-TEQ</b>	<b>Seveso Mothers TEQ Concentration in Milk at Birth (pg/g lipids)</b>	<b>Seveso Mothers TEQ Concentration in Milk 3 Months After Birth (pg/g lipids)</b>
TCDD	4.45	3.70
PCDD/PCDF TCDD-TEQ	11.80	10.67
PCB TCDD TEQ	5.57	6.02
Total TCDD-TEQ	17.37	16.67

In both milk samples the concentration of TCDD-TEQ exceeds the TCDD concentration by about four-fold. Congener profiles are provided as is a comparison with mother's milk from Milan and a rural area. The TCDD levels in the milk from Seveso mother's was elevated compared to mothers from Milan and the rural area, but the fact remains that mother's milk from the contaminated zones around the site of the 1976 Seveso explosion contain levels of TCDD-TEQ that far exceed the levels of TCDD alone.

Baccarelli et al. (2008) measured the levels of PCDD, PCDF, and co-planar PCBs in plasma of 51 Seveso, Italy women from 1994 to 2005. According to Baccarelli et al. (2008): "Maternal mean TCDD levels were 18.9 ppt (n = 51, range 1.4–309.5). Mean plasma TEQs were 44.8 ppt (n = 51, range 11.6–330.4) for PCDDs, PCDFs, and coplanar PCBs;..." Their Figure 2 provides plots of maternal plasma TCDD versus neonatal TSH in offspring and maternal PCDDs, PCDFs, and cPCBs versus neonatal TSH in offspring. The plots clearly show that most women's TCDD levels were 2.5 to 10 ppt, whereas the TCDD-TEQ levels were 20 to 60 ppt. Thus, TCDD comprised only a small fraction of their total TEQ concentration, and neonates were exposed to far more TCDD-TEQ than they were to merely TCDD.

Eskenazi et al. (2004) measured PCDD, PCDF, and co-planar PCBs in pooled archived serum samples from 180 females living in non-ABR zones taken in 1976.

**TABLE 3  
TCDD-TEQ DATA FROM ESKENAZI ET AL. (2004)**

<b>Analytes</b>	<b>Concentration (ppt)</b>
TCDD	20.2
Total TCDD-TEQ	100.4

The concentration of TCDD-TEQ in serum samples from 1976 from the women living near but not within the Seveso contaminated zones was about five-fold higher than the concentration of TCDD alone. Thus, total TCDD-TEQ concentrations in background exposures from non-TCDD compounds is significant. Such exposures to background dioxin-like compounds apply to people living in the A, B and R zones, as well.

Collins et al. (2006) measured the PCDD, PCDF, and co-planar PCBs in serum of 62 workers exposed to chlorophenols and 36 workers in the same plant without chlorophenol exposures. Levels of total TCDD-TEQ were 4-5 times higher than levels of TCDD alone in these workers.

**TABLE 4  
TCDD-TEQ DATA FROM COLLINS ET AL. (2006)**

<b>Subjects</b>	<b>TCDD (ppt)</b>	<b>TCDD-TEQ (ppt)</b>
Chlorophenol workers	16.7	68.4
Non chlorophenol workers	6.0	32.7

Collins et al. (2008) measured the PCDD, PCDF, and co-planar PCBs in serum of 98 workers some of whom were exposed to trichlorophenol, pentachlorophenol or both. Levels of total TCDD-TEQ were 2-7 times higher than levels of TCDD alone in these workers.

**TABLE 5  
TCDD-TEQ DATA FROM COLLINS ET AL. (2008)**

<b>Subjects</b>	<b>TCDD</b>	<b>% of total TCDD-TEQ caused by TCDD</b>
Chlorophenol workers	7.8	12.2
Pentachlorophenol workers	36.8	37.0
Chlorophenol + pentachlorophenol workers	13.3	17.6
Tradesmen	20.7	21.6
Reference Group	6.0	15

In conclusion, for EPA to claim with any credibility that it is using the “best available science” in finalizing its risk assessment of dioxin and dioxin-like compounds, it must abandon its exclusive and misleading focus on TCDD and perform dose-response assessment on total TCDD-TEQ.

Mocarelli et al. (2008) recognize this issue as noted below: “If TCDD acts in concert with other dioxin-like chemicals in affecting sperm quality, the total dioxin toxic

equivalency (TEQ) should be considered. In nine serum pools from females residing in the uncontaminated area in 1976, Eskenazi et al. (2004) found an average TEQ of 100 ppt." Also: "TCDD and other dioxin-like chemicals produce their effects primarily through the aryl hydrocarbon receptor (AhR)." [emphasis added]

**Comment 2: The proposed RfD is excessively stringent (low) and cannot be based on the "best available science," because the "real-world" health effects it would have predicted over the last several decades have not been observed. Background mean intakes of PCDD/Fs and PCBs in the U.S. population during the 1960s, 1970s, 1980s, and throughout much of 1990s exceeded the proposed RfD of 0.7 pg/kg-day by 30-fold or more. Therefore, the adverse health outcomes upon which the RfD is based, thyroid hormone modulation (and accompanying effects) and lowered sperm count (and motility), would have been observed in the general population if the RfD was accurate. However, there is no evidence that such effects were observed. To the contrary, increasing trends in measures of thyroid hormone status and sperm quality throughout the last 20 years run exactly opposite to the substantial declines in background dioxin exposures that have been observed during this same time period.**

The RfD resulting from the EPA's reassessment will have major implications for the human health risk assessment of dioxin and furan congeners in all media. It is critical that EPA assess the scientific credibility of their proposed toxicity values to determine if they make any sense in the context of "real-world" effects on health. EPA routinely requires that validation exercises be performed whenever a mathematical or biologically-based model is developed. Furthermore, in its Charge to External Reviewers, EPA (2010b) specifically asks the reviewers to comment on whether EPA applied "the epidemiology and animal bioassay study criteria/considerations in a scientifically sound manner." Accordingly, the EPA should attempt to validate the predicted toxicological effects for the U.S. population, to determine if the draft RfD is scientifically sound.

Typical daily intakes of PCDD/Fs and PCBs (as toxicity equivalents [TEQ]) in the U.S. population are well documented. The major sources are animal products in the food supply. Average daily intakes have been declining from a peak in the 1960s when intakes were likely as high as 15-20 pg/kg-day (Pinsky and Lorber, 1992) to the current estimated intakes of < 1 pg/kg-day (EPA, 2009; Aylward et al., 2008). As shown in Table 6, background intake levels steadily declined through this time period, but were at levels substantially higher than EPA's proposed RfD of 0.7 pg/kg-day for a period of 30 years or longer. It is noted that where Table 6 shows mean intake levels, upper 99% percentile intakes, according to EPA (Reassessment, Part III, p. 4-19; 2010a), have likely been 3 times higher.

**TABLE 6  
MEAN (BACKGROUND) U.S. DIOXIN INTAKES AND  
HAZARD INDICES BASED ON PROPOSED USEPA RFD**

Time Period	Mean serum (Lipid) Levels (ppt TEQ)	Intake (TEQ Dose) pg/kg-day <sup>a</sup>	Hazard Indices (Dose/0.7 pg/kg-day)
2005 - present	9.2 <sup>a</sup>	<1 <sup>a</sup> <1 <sup>b</sup>	~1 ~1
1995 – 2005	13 – 25 <sup>c</sup>	2 – 4 <sup>c,e</sup>	3 - 6
1990 - 1995	25 - 33 <sup>c</sup>	4 – 5 <sup>c,e</sup>	6 – 7
1980s	42 - 51 <sup>c</sup>	5 – 8 <sup>c,e</sup>	7 - 11
1970s	75 – 82 <sup>c</sup>	8 – 13 <sup>c,e</sup>	11 - 19
1960s	~100 <sup>d</sup>	~16 <sup>d,e</sup>	~23
1950s	~66 <sup>d</sup>	~11 <sup>d,e</sup>	~16

Notes:

<sup>a</sup> U.S.EPA (2009a); Aylward et al. (2008), citing UMDES (2008).

<sup>b</sup> Lorber (2010)

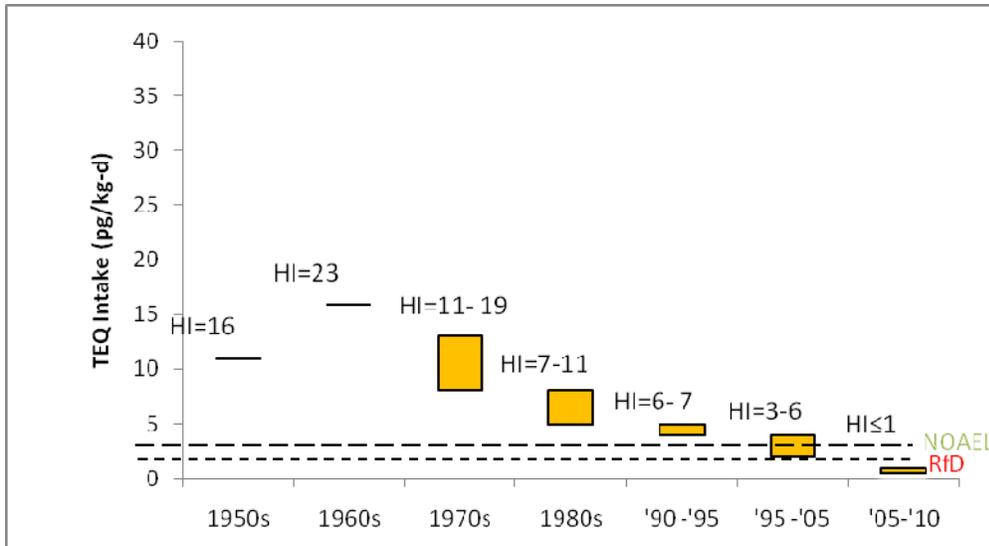
<sup>c</sup>Data from Hays and Aylward (2003). PCDD + 2,3,4,7,8-PeCDF TEQ values.

<sup>d</sup> Data from Hays and Aylward (2003). PCDD + 2,3,4,7,8-PeCDF TEQ values, scaled in accordance with Lorber (2002) Figure 6.

<sup>e</sup> Estimated from mean serum lipid TEQ figures and method of Steenland et al. (2001), which assumes steady-state conditions and 30% body fat. PCDD + 2,3,4,7,8-PeCDF TEQ values were multiplied by 1.6 to approximate total TEQ values including dioxin-like PCBs (Hays and Aylward (2003)).

These same data are graphically depicted in the following figure.

**FIGURE 1  
NORMAL BACKGROUND TEQ (PCDD/F, PCB) INTAKES IN U.S. POPULATION  
VERSUS EPA PROPOSED RFD AND ESTIMATES OF A HAZARD INDEX**

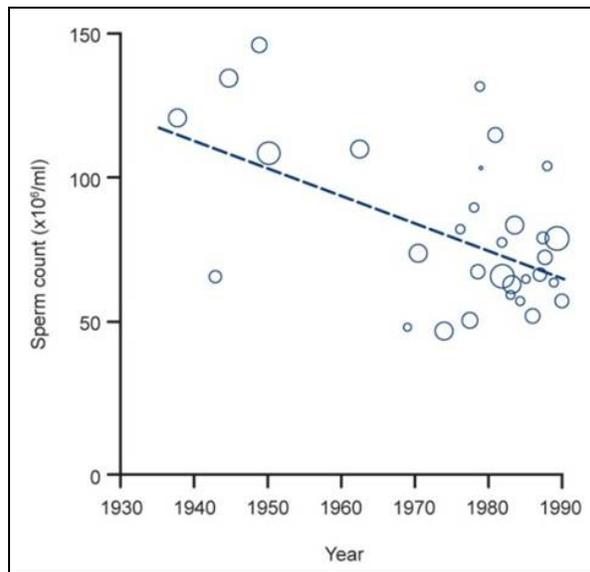


Using the intake data in Table 6, a range of hazard index (HI) values have been calculated using the proposed RfD for each time period shown. The HIs for average population ranges from 21-29 in the 1960s to 1-3 for the period 1995-2005. HI values for 99<sup>th</sup> percentile intake levels could be 3 or more times higher (EPA, 2000). Based on this assumption, the general population experienced HI values in the range of 3 to 30 for 30 or more years from the 1960s through the 1990s.

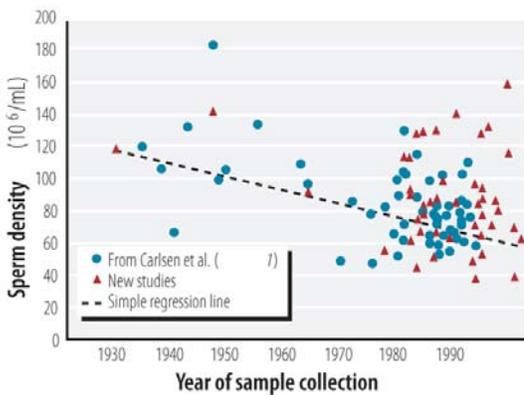
The theoretical adverse health effects that EPA would have expected from these high HIs are the critical effects chosen by EPA for the RfD derivation. The first critical effect chosen by EPA is a decrease in sperm count and motility in young men (22-31 year old) exposed as children (1-9 years old) (Mocarelli et al., 2008). Several studies examining sperm count and motile sperm count in various human populations during pertinent time periods are available.

Now-refuted but widely cited studies have reported worldwide decreases in sperm quality (Carlsen et al., 1992; Swan et al., 1997, 2000). These studies report a decline that purportedly follows a gradual, continual decrease in sperm concentration throughout the period, 1940 to 1990, with no observed minimum seen in the 1960s, the period coinciding with peak background dioxin exposures.

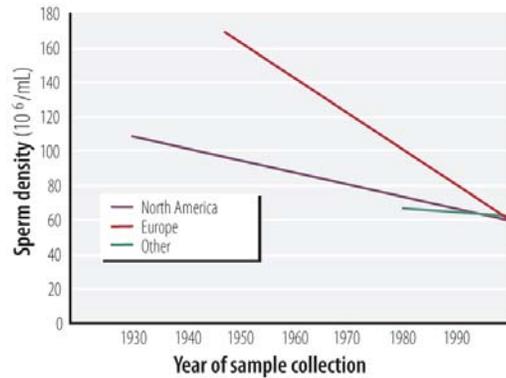
**FIGURE 2**  
**REPORTED LONG-TERM DOWNWARD TREND IN SPERM COUNTS BASED ON DATA COLLECTED FROM VARIOUS REGIONS ACROSS THE GLOBE (FROM CARLSEN ET AL., 1992)**



**FIGURE 3**  
**REPORTED LONG-TERM DOWNWARD TREND IN SPERM COUNTS BASED ON**  
**DATA COLLECTED FROM VARIOUS REGIONS ACROSS THE GLOBE**  
**(FROM SWAN ET AL., 2000)**



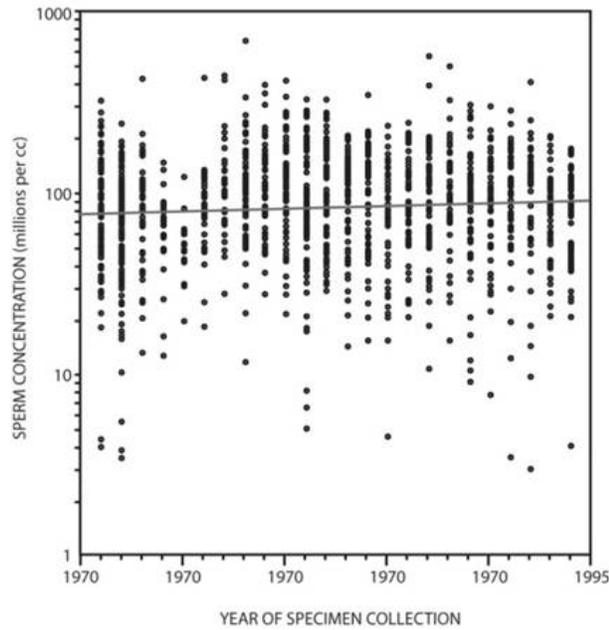
Mean sperm density in 101 studies published 1934–1996 and simple regression line.



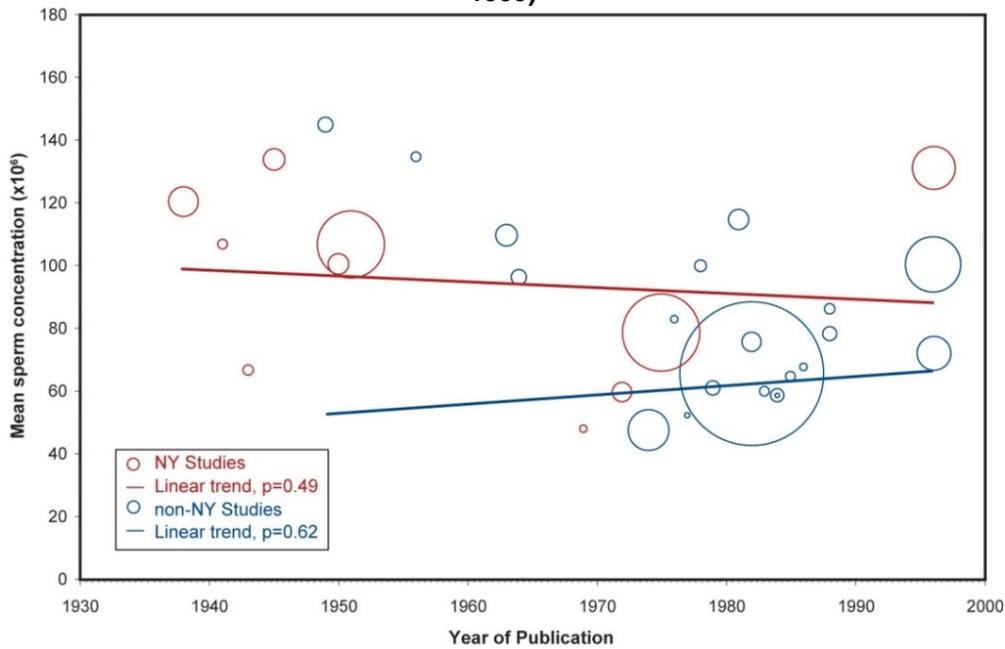
Interactive regression model for mean sperm density by year and geographic region, after controlling for proven fertility, abstinence time, age, specimen collection method, method of counting sperm, whether the study was included by Carlsen et al. (1), and interaction of region and study year.

However, many other studies have thoroughly refuted the studies of Carlsen, Swan and others when the confounding effects, including that of geography are controlled. These more carefully controlled studies have failed to corroborate the decreasing trend in sperm count (and motility) claimed by Carlsen and Swan et al. (Bromwich et al. 1994; Fisch et al., 1996; Fisch and Goluboff, 1996; Emanuel et al. 1998; Saidi et al. 1999; Acacio et al. 2000; Fisch 2008; MacLeod and Wang, 1979; Younglai et al., 2000). These other studies report relatively little, if any, change in sperm counts throughout this time period.

**FIGURE 4**  
**SPERM CONCENTRATION DATA PLOTTED YEARLY (1970-1995)**  
**SHOWS NO DECLINE (FROM FISCH ET AL., 1996)**

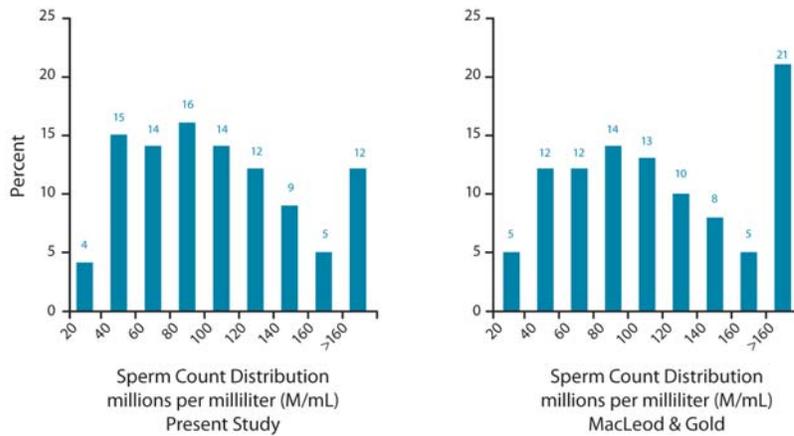


**FIGURE 5  
META-ANALYSIS OF SPERM COUNT DATA FROM REGIONS INSIDE VS. OUTSIDE NEW YORK STATE SHOWS NO DECLINE (FROM SAIDI ET AL., 1999)**



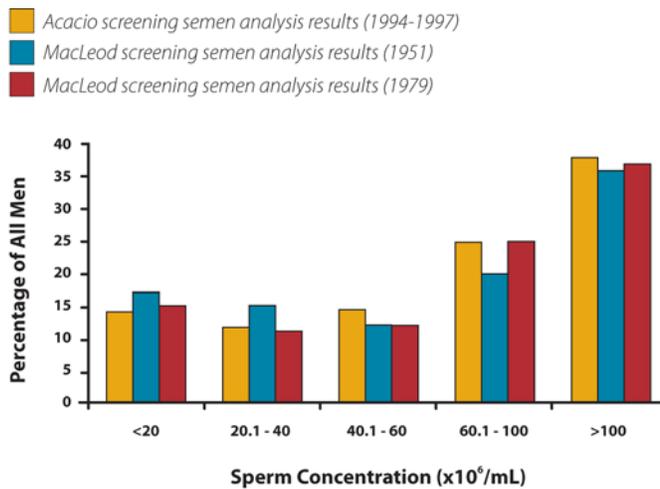
Sperm counts in U.S. Bubble size corresponds to number of men in study

**FIGURE 6  
COMPARISON OF SPERM COUNT DATA FROM MINNESOTA MEN (1971-1994)  
TO 1951 STUDY BY MACLEOD AND GOLD SHOWING NO DECLINE  
(FROM EMANUEL ET AL. 1998)**



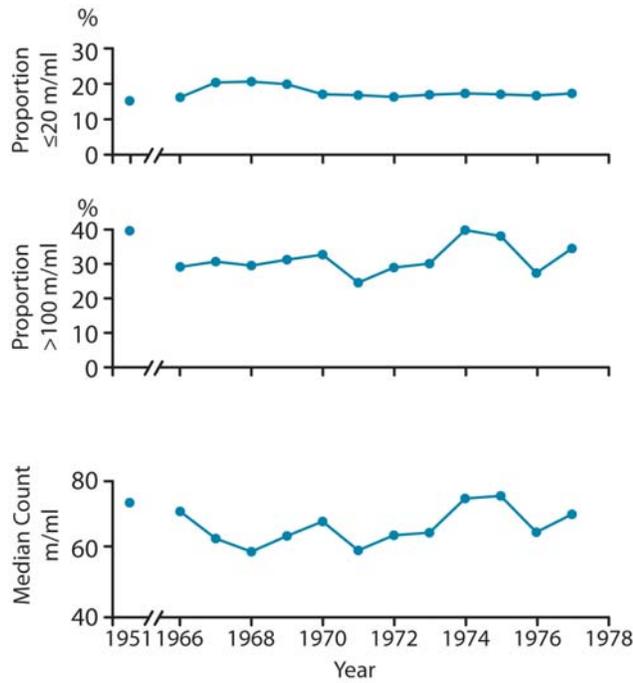
Sperm count distributions (percent of patients with sperm count below each increment of 20 x 10<sup>6</sup>/mL).

**FIGURE 7  
RESULTS OF THREE STUDIES SHOW NO DECLINE FROM 1951 TO 1997  
(FROM ACACIO ET AL., 2000)**



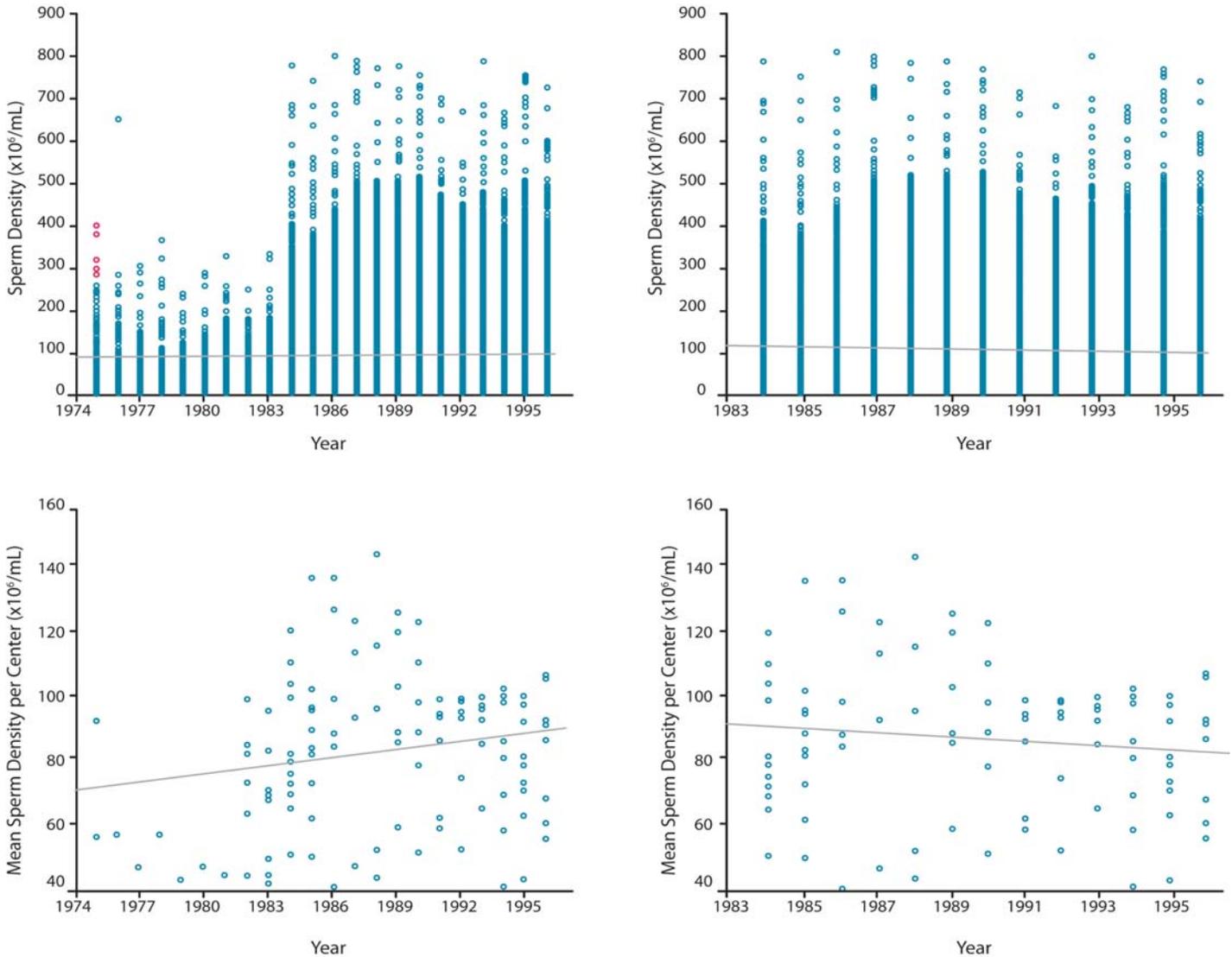
Acacio. Screening semen analysis. Fertil Steril 2000.

**FIGURE 8  
COMPARISON OF MACLEOD AND GOLD RESULTS  
FROM 1951 TO A SIMILAR POPULATION IN 1966 TO 1977  
(FROM MACLEOD AND WANG, 1979)**



Median sperm counts (millions per milliliter) and extremes of count frequency distributions of composite infertile populations yearly from MacLeod laboratory 1966 to 1977 as compared with similar population of MacLeod in 1951.

**FIGURE 9  
SPERM COUNT DATA IN CANADIAN MEN 1974 – 1995  
(FROM YOUNGLAI ET AL., 1998)**

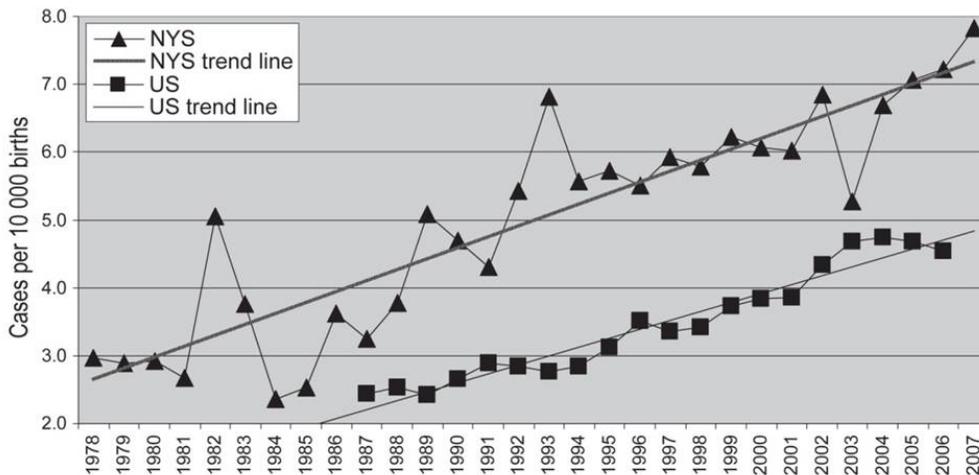


In sum, the available evidence demonstrates an unchanged trend in sperm quality in the U.S. over the time period when background TCDD intakes declined substantially. Using the proposed EPA RfD, peak background intakes in the 1960s predicts as much as a 20% decrease in sperm concentration. However, there is no evidence for any such effect in the general population.

The second critical effect chosen by EPA was an increase in thyroid stimulating hormone (TSH) levels in neonates due to maternal dioxin exposure (Baccarelli et al., 2008). Massive screening programs have measured TSH levels in newborns throughout most areas of the globe since the 1970s. The data have not been assembled for the purpose of analyzing population-level effects, and few data with reasonable detection limits are available for earlier time periods. However, neither Baccarelli et al. (2008) nor EPA (2010a) has presented any data that shows increasing TSH levels in the population during the years when dioxin exposures were high and decreasing levels in more recent years, specifically the last 20 years.

Further, the modest increases in TSH observed by Baccarelli et al. (2008), purportedly caused by TCDD, would be unlikely to cause clinical hypothyroidism in newborns. Lott et al. (2004) found no confirmed cases of hypothyroidism in newborns with a TSH of <29 uU/mL from among a population of 161,244 newborns. However, in choosing neonatal TSH as a critical endpoint in the RfD derivation, EPA expressed concern over this endpoint and suggested that dioxin exposures could cause hypothyroidism in newborns of a severity sufficient to cause neurodevelopmental effects. Therefore, it is interesting to note that the reported incidence of congenital hypothyroidism (CH), which is the health outcome that is the primary concern of TSH screening of neonates, has been *increasing* since the 1980s. In other words, the incidence of CH has not declined in parallel with the declining exposures to dioxin in the U.S. In fact, CH has actually been increasing during the past 20 years. CH incidence has increased from 1:4100 in 1987 to 1:2350 in 2002, an increase of 73 percent (Hinton et al., 2010). Thus, the primary health outcome of concern associated with neonatal TSH levels (i.e., CH) is exhibiting a population-level trend that runs counter to the declining dioxin intakes in the U.S.

**FIGURE 10**  
**LONG-TERM INCREASES IN THE PREVALENCE OF CONGENITAL HYPOTHYROIDISM (CH) BASED ON NEONATAL SCREENING DATA FROM NEW YORK STATE AND THE U.S. (FROM HINTON ET AL., 2010)**



In summary, average population TCDD-TEQ exposure levels for several decades of the 1900s far exceeded the proposed RfD, predicting that substantial portion of the U.S. population should have exhibited observable increases in TSH levels > 5 µU/mL and observable decreases in semen quality (20% decrease in sperm concentration and a 11% decrease in total motile concentration), if EPA's RfD is a realistic predictor of adverse effects in humans. However, not only are there are no data to indicate that this was the case, but the available data on the critical endpoints (TSH levels, sperm counts) indicate that, where long-term trends in these human health indicators have been measured, the trends run exactly counter to the declining levels of background TEQ intake.

**Comment 3: EPA's proposed OSF is unreasonably high and cannot be based on the "best available science" because the "real-world" health effects it would have predicted over the last several decades have not been observed. The proposed OSF predicts that more than 100% of all bladder and larynx cancer in the entire US population is caused by dioxin.**

As noted in the above comment, average daily intakes have been declining from a peak in the 1960s when intakes of total TCDD-TEQ including dioxin-like PCBs were likely as high as 16 pg/kg-day (Hayes and Alward, 2003) to the current estimated intakes of < 1 pg/kg-day (EPA 2009); Aylward et al. 2008). As can be seen in Table 6, it is not unreasonable to assume that the average dose of TCDD-TEQ for Americans

over the period 1930 to 2000 was about 8 pg/kg-day. Assuming the proposed OSF of  $1 \times 10^6$  per (mg/kg-day), the estimated cancer risk for an average American over the seventy year period from 1930-2000 is  $8 \times 10^{-3}$ . If this proposed OSF is a true predictor of human risk, then almost 1% of all Americans exposed to typical TCDD-TEQ doses from the 1930s through the 1990's would have been expected to contract cancer from dioxin-like compounds over this period.

The average U.S. population from 1970-2000, reflecting the population from the 1960's through the 1990's was 240,180,239. Thus, the total cancers estimated from exposure to TCDD-TEQ over the 70 year period from 1930 to 2000 was  $1.9 \times 10^6$  or 27,000 per year assuming an estimated excess lifetime risk of  $8 \times 10^{-3}$ .

Cheng et al. (2006) have reported that the only two sites that were statistically significantly elevated in the dioxin worker cohorts were increased mortality rates for larynx cancer and bladder cancer. According to the National Cancer Institute SEER statistics (<http://seer.cancer.gov/faststats/selections.php?#>), the mortality rates for these two cancers in 2000 were as follows.

Larynx =	1.3861 per 100,000
Urinary bladder =	4.3202 per 100,000

Assuming the population of 282,171,957 for the year 2000, these incidence rates translate into the following number of cases:

Larynx =	3,911 deaths/year
Urinary bladder =	12,190 deaths/year
Total	16,101 deaths/year

This screening level validation exercise is presented to demonstrate that if the proposed OSF for dioxin based on increased mortality for cancer of the larynx and the bladder is a valid predictor of human health risk, then the logical conclusion that must be drawn is that exposure to dioxin and dioxin-like compounds must be responsible for more deaths from larynx and bladder cancer per year than there actually are in the entire population.

This is a troubling result considering that both of these cancers have well-defined risk factors that must be the cause of the majority of these cancers, as noted below:

**TABLE 7  
KNOWN RISK FACTORS FOR BLADDER AND LARYNX CANCER**

<b>Cancer Site</b>	<b>Known Risk Factors</b>
Bladder Cancer	Smoking Aromatic Amines Cancer Treatment Family History
Larynx Cancer	Smoking Alcohol Poor Dental Hygiene HPV Virus Asbestos Dietary Deficiency

Cheng et al. were aware of this very same issue as noted below:

“Application of the incremental risk estimates from Table IV to general population serum lipid TCDD levels suggests that the lifetime cancer mortality risk that may be attributable to background TCDD exposures is below 1 in 10,000....older individuals might have incremental risks as much as 10 times higher.”

**Comment 4: Revision of the current Oral Cancer Slope Factor (OSF) and issuance of a Reference Dose (RfD) for TCDD is not necessary and will not result in an appreciable reduction in health risks.**

A review of the currently available science indicates that there is no need to take regulatory action to change toxicological criteria used currently to evaluate dioxin levels in environmental media. There is substantial evidence to indicate that environmental emissions, concentrations in foods, and human serum levels of these compounds have been decreasing consistently since the 1970s, due to changes in environmental practices and measures that have already been undertaken by industry and regulators to eliminate dioxin containing products and reduce some avoidable emissions. In addition, there is substantial evidence to indicate that exposure via direct contact with TCDD-TEQ in soil is a very minor exposure pathway. Thus, even if TCDD-TEQ concentrations in soils were reduced as would be required by the issuance of these new toxicological criteria, there would be no appreciable changes in body burdens and thus little to no net benefit in terms of the protection of human health. Finally, there is a substantial body of data available that demonstrate that even when exposures to current levels of dioxin are believed to occur, there does not appear to be an increase in body burdens, indicating that current intake rates do not exceed rates of elimination.

### Reduction in TCDD-TEQ Concentrations

The EPA's dioxin reassessment (EPA 2003a) and other sources of scientific data demonstrate that TCDD-TEQ releases to the environment and levels in the human diet and in blood have decreased dramatically since the early 1970s. These reduced releases to the environment are the result of improved technologies and the development of alternative industrial processes. The net result has been that levels of TCDD-TEQ in humans have been substantially reduced since these activities were initiated and, because of the long half life of most of these compounds, it is expected that levels will continue to decrease, even if current intake levels are not reduced. This reduced body burden is clearly demonstrated in younger segments of the United States population who have not had exposure to historical levels of TCDD-TEQ and who have body burdens well below the levels that might be associated with adverse health effects.

EPA (2003a) reported that releases of dioxin-like compounds decreased by 80 percent between 1987 and 1995 as a result of reduced point source emissions from municipal and medical waste incinerators. They estimated that the release of 14,000 grams (g) of TCDD-TEQ/year in 1987 decreased to approximately 3,300 g of TCDD-TEQ/year in 1995. In addition, EPA estimated that yearly emissions would continue to decline, resulting in emissions of 1,500 g TCDD-TEQ in 2005 or approximately a 10-fold decrease from the 1987 level, as a result of changes in technology.

These changes in emissions have resulted in changes in TCDD-TEQ levels in foods. EPA (2003a) provided estimates of dietary intake of TCDD-TEQ for 1994 and 2000. The reported intake level of 0.6 picograms per kilograms-day (pg/kg-day) for the year 2000 was lower by 66 percent than the estimated intake level of 1.7 pg/kg-day reported for 1994. Similarly, Winters et al. (1998) reported that preserved meat from the 1940s through the 1970s had dioxin/furan concentrations that were two to three times higher than did samples of meat from the mid-1990s.

Similar trends have been reported in Europe because of reduction of emissions there. Hays and Aylward (2003) reported that mean intakes of polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) by adults in the United Kingdom dropped from 7.2 pg TCDD-TEQ/kg-day in 1982, to 2.5 pg TCDD-TEQ/kg-day in 1992, to 1.8 pg TCDD-TEQ/kg-day in 1997. Similar patterns were observed when PCDD/Fs were considered alone and when populations in the Netherlands and Germany were evaluated (Hays and Aylward 2003).

These reduced emissions and reduced levels in foods have resulted in substantially decreased body burdens of TCDD-TEQ in humans. The Agency for Toxic Substances

and Disease Registry (ATSDR 2005) reported that body burdens of dioxin and dioxin-like compounds measured in blood and adipose tissue have dropped steadily in the United States over the past several decades, from 50 to 80 ppt TCDD-TEQ in the 1970s, to 30 to 50 ppt TCDD-TEQ in the 1980s, to 10 to 20 ppt TCDD-TEQ in the 1990s. They report that current levels of TCDD-TEQ range from 3 to 10 ppt in the general population and rarely exceed 10 ppt.

Also, ATSDR demonstrated a drop in serum levels over an eight-year period in a study that compared serum TCDD-TEQ concentrations, which were measured in 1998 and again in 2006 in a group of residents living in Mossville, Louisiana. These studies showed that between 1998 and 2006, serum dioxin concentrations had decreased in most participants, indicating that their rates of intake were less than their rates of elimination, despite living in an area known to have had substantial dioxin releases. ATSDR indicated that while the older participants had elevated blood levels compared to the general United States population, it did not expect these concentrations to result in adverse health effects. They also concluded that the elevated blood dioxin levels in those individuals were likely the result of past, rather than current, exposures (ATSDR 2005).

Further, Jackson and Michalek (2001) evaluated temporal changes in TCDD concentrations in Air Force Vietnam veterans who served as the non-exposed comparison group in the study of the effects of herbicide exposure to individuals involved in Operation Ranch Hand. Serum concentrations in this comparison group were measured in 1987, 1992 and 1997. The mean TCDD concentration in 1987 was 4.5 ppt, while the value dropped to 3.2 ppt in 1992 and 2.0 ppt by 1997. Maximum measured concentrations decreased from 26.6 ppt in 1987, to 12.2 ppt in 1992, and 10.2 ppt in 1997. These authors reported that the TCDD levels decreased significantly with time, with an average drop in mean levels of 6.6 percent per year. The rate of decrease was estimated to be approximately 0.25 ppt per year. These decreases were observed even though the mean age of these individuals increased. Generally, TCDD levels tend to increase with age, due to cumulative exposure (EPA 2003a; ATSDR 2005), so this evaluation indicates that exposures had decreased substantially so that TCDD was being eliminated more quickly than it was being absorbed.

Two studies conducted for German populations demonstrated the same trends. Furst (2006) evaluated changes in concentrations of dioxins and selected PCBs in human milk in Germany over time. This author found that the levels of dioxins and furans decreased substantially in a period of 14 years. While human milk samples collected in 1989 contained 33.9 pg TCDD-TEQ /g fat, in 2003 the measured concentrations had decreased to 9.8 pg TCDD-TEQ /g fat. This was a decrease of 71 percent. Similar patterns were observed for PCBs with the median daily exposure through

breastfeeding decreasing from 7,000 nanograms per kilogram body weight (ng/kg bw) in 1984 to 1,300 ng/kg bw in 2003, a decrease of 81 percent.

Wittsiepe et al. (2000) evaluated human blood levels of dioxins and furans in Germany between 1989 and 1998. These authors reported that they observed a consistent decrease in blood levels. While the mean level found in 1989 was 43.7 pg TCDD-TEQ /g fat [International TEQ, see EPA (1989)], that level decreased to 20.7 pg TCDD-TEQ (International)/g fat in 1996/1998. They found that the reduction by roughly 50 percent was observed for most congeners, for the sums of congeners and for the calculated TCDD-TEQ concentrations.

Aylward and Hays (2002) evaluated temporal trends in human body burdens of dioxin over three decades. These authors collected information from studies that reported levels of TCDD in human populations of the United States, Canada, Germany, and France from the 1970s to the present. Their evaluation of these data demonstrated that there has been a consistent decrease in lipid levels of TCDD between 1972 and 2000 resulting in a 10-fold decrease over that period. They reported that lipid-adjusted TCDD levels in the year 2000 were approximately 2 ppt. They also reported that these data, along with the long half-life for TCDD in humans, appear to indicate that these decreases have occurred as a result of substantial decreases in intake levels.

Aylward and Hays (2002) used pharmacokinetic modeling to estimate that the mean serum lipid TCDD level in the general population will be 1 ppt or less by the year 2015, even if intake levels do not decrease further. They reported that intakes have been reduced because of changes in environmental practices, such as prohibition of open burning in landfills, reduced herbicide usage, improved technology and stricter regulations on combustor emissions. They estimated that current intake levels do not exceed 0.04 pg/kg-day, which is well below the dose-response criterion used to develop the soon-to-be-released Interim Final PRG.

Hays and Aylward (2003) reported that while emissions of TCDD-TEQ have decreased substantially over time, as have intake levels, body burdens have not yet fully demonstrated the impact of these reductions due to the long elimination half life of TCDD and many of the related congeners. They suggested that, because of the long half life for these compounds, dramatic decreases in intake levels must have occurred, and it is likely that the levels in the general population of the United States have not yet declined to the levels that will reflect steady state at the current levels of intake. Levels in the population will lag as levels in the environment, and consequently in the food supply, continue to decrease. Thus, while reductions in body burdens have been substantial to date, they will continue to decline. They concluded that the measures that have already been taken to control releases and sources have reduced exposure

to levels that would likely have occurred in the early 1900s. In addition, while further reductions are expected, the impact of those reductions on body burdens will likely have less impact due to the fact that body burdens have already decreased substantially (Hays and Aylward 2003), and there will continue to be natural sources of dioxins and furans in the environment to which individuals will be exposed.

LaKind et al. (2009) evaluated National Health and Nutrition Examination Survey (NHANES) data for the United States population between 1999 and 2004 to determine if there were temporal trends in blood levels of TCDD-TEQ. While the analysis was somewhat compromised by the fact that there were a large number of non-detected values, and the changing detection limits over time affected the analysis, these authors concluded that a review of these five years of data indicated that serum levels decreased by 56 percent for the 12 to 19 year old group, and by 38 percent for the 20 to 39 year old group. There was a slight non-significant decrease observed for individuals between 40 and 59 years of age and a slight significant increase for individuals 60 years and older. They acknowledged that there are difficulties in making these comparisons because the relationships between reduced emissions and declining levels in the environment on changes in levels in human serum are complicated by the half-lives of these compounds, natural sources of the compounds, changes in analytical methodologies and changes in detection limits.

LaKind et al. (2009) concluded that while levels appear to have not decreased substantially in the older portions of the population, they have declined in the younger segments of the population. Given the guidance values upon which regulatory decisions are made are based on the avoidance of developmental effects in offspring, it is important to evaluate levels in children and adults of reproductive age. LaKind et al. (2009) reported that the mean TCDD-TEQ for those individuals aged 12 to 29 (at or approaching reproductive age), are lower than the biomonitoring equivalents (BE) that they calculated. These BEs are the estimated serum concentrations that are associated with regulatory guidance levels. LaKind et al. (2009) calculated BEs of between 15 and 70 ng/kg for serum based on the ATSDR's Minimum Risk Level (MRL), the Joint Expert Committee on Food Additives Provisional Tolerable Monthly Intake, the European Commission Scientific Committee on Foods Tolerable Weekly Intake and the United Kingdom Committee on Toxicology's Tolerable Daily Intake. Mean serum concentrations reported by LaKind et al. (2009), based on the NHANES data for the 12 to 19, 20 to 39 and 40 to 59 year old age groups, were all below those levels, indicating that there was a low likelihood of adverse effects given current body burdens in those age groups.

In summary, the nine studies cited above demonstrate that dioxin and furan concentrations in U.S. and European foodstuffs and human tissues have been

consistently decreasing over the last several decades. These concentrations will continue to decrease over time, indicating that there is no public health imperative to propose new toxicological criteria for dioxins and furans at this time.

#### Soil as a Minor Contributor to Exposure

Soil is a minor contributor to total exposure to TCDD-TEQ in the environment with food products (particularly meat, fish and dairy products) providing the most substantial contribution to exposure (Travis and Hattemer-Frey 1991; Henry et al. 1992; EPA 2003a; Aylward and Hays 2002; Harrad et al. 2003). As a result, even if the target soil concentrations, were reduced to the levels that would result from EPA's proposed OSF and RfD, and soils were actually remediated to those levels, the overall background exposures would not be meaningfully reduced.

Part 1, Chapter 4 of the EPA's 2003 draft Dioxin Reassessment (EPA, 2003a) provides a discussion of the sources of intake of dioxins in the human population. It provides information on the contribution of different exposure routes on background levels of exposure to adults and children in the United States as well as in other parts of the world. This analysis consistently points to soil ingestion and soil dermal contact being very minor contributors to overall exposure to TCDD-TEQ in the environment.

Using the World Health Organization (WHO) TEQ approach, EPA estimated mean daily intakes by a number of direct contact and food ingestion pathways. As shown in Tables 4-30 and 4-31 of that report, direct contact with soil (ingestion and dermal contact) by adults was estimated to account for only 1.4 percent of total TCDD-TEQ exposures in the United States, and less than 0.1 percent of total exposures to dioxin-like PCB TEQ. While exposure to young children (aged 1 to 5) was assumed to be higher due to higher soil ingestion rates and lower body weights, overall direct contact with soil by this age group was estimated to contribute only 2.6 percent of total exposure (EPA 2000a, Table 4-34). The majority of the remaining exposures were the result of food consumption, including fish, milk, dairy, eggs, beef, pork, poultry and vegetable fat.

This pattern has remained consistent over time. As presented by EPA (2003a), a study of sources of exposure to TCDD-TEQ conducted in 1991 by Travis and Hattemer-Frey indicated that 94 percent of total intake was due to food ingestion while a study conducted by Henry et al. 1992 (reported in EPA 2003a) indicated that 99 percent of dioxin intake was due to food consumption. EPA's (2003a) reassessment document indicated that 91 percent of the estimated total intake at the time of the reassessment (5.6 pg/day) was due to food consumption, and the other 9 percent was due to "other" factors. While soil ingestion would be included in the "other" category, EPA did not

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specify what the other sources of exposure might be. In a minority of cases, residential soils may be used for backyard gardening, and dioxin and furans in soils may contribute to individuals' overall food consumption intakes of dioxins and furans. Even in such cases, however, the majority of dioxin intake from the food chain is attributed to foods grown elsewhere and this intake is completely unaffected by the dioxin content of soils in areas proximate to the receptor.

There are a number of high-quality studies that provide evidence that there is little or no correlation between soil concentrations and body burdens of TCDD-TEQ in the individuals exposed to those soils. This lack of correlation was clearly demonstrated in the recent University of Michigan population-based human exposure study. This study was designed to identify whether there was a relationship between levels of dioxins, furans, and selected PCBs in soil and household dust, with blood serum concentrations of those compounds in the individuals exposed to them (University of Michigan 2006). A total of 946 individuals were included in the study, including individuals from four zones near the Dow Chemical facility in Midland, Michigan, and a reference area in Jackson and Calhoun Counties, which was more than 100 miles away from the Dow Chemical facility. Blood samples were collected from those individuals as were samples of soils surrounding and dusts inside their homes. In addition, participants were asked to complete a questionnaire that included information about their demographic characteristics, personal factors such as smoking, body mass indices, and breastfeeding behavior, whether they had ever worked for Dow Chemical, whether they participated in fishing, hunting or other recreational activities in the area and whether they consumed a variety of food products.

Blood levels of the 29 dioxin, furan and PCB congeners for which toxicity equivalency factors have been developed were evaluated and compared with a number of environmental and behavioral characteristics. While some of the soil and dust concentrations measured were in low ppb, ranging up to 15 ppb, these concentrations were not good predictors of the body burden levels in the individuals who were exposed to them. Although the people who lived near the Dow facility had higher levels of these compounds in their blood than were measured in the reference population (which had levels similar to the concentrations in the general United States population), Garabrant et al. (2009) reported that soil and household dust content only explained approximately 0.5 percent of the variability in serum levels of TCDD, 1 percent for PCB-126, and <0.01 percent for all the other congeners.

The greatest variations in blood levels were explained by age, sex, body mass index, weight loss, breast-feeding and smoking. The study reported that age is the most important factor affecting blood serum levels of these compounds and that this was true regardless of whether the individuals lived in either the study or the reference area.

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It concluded that there was no relationship between measured serum dioxin levels and the soil/dust concentrations to which individuals were exposed, and that historic exposures to these compounds were of greater importance than current levels of exposure (Garabrant et al. 2009).

These data indicate that even if soil levels were reduced substantially, it is unlikely that such reductions would have a corresponding impact on reductions in body burdens within the exposed population. Consequently, there would be very little reduction in potential health risks to the exposed populations if the toxicological criteria were changed as proposed.

A similar disconnect concerning the relationship between expected levels of exposure and measured body burdens was reported in the ATSDR study conducted in Louisiana in 2005. ATSDR evaluated the TCDD-TEQ blood serum levels in residents of Calcasieu Parish, Louisiana, which is a highly industrialized area where there were known releases of dioxin. This study was a followup to a 1998 evaluation of individuals living in Mossville, an area of Calcasieu Parish, in which some individuals had demonstrated elevated blood levels of dioxin. The purpose of the 2005 study was to determine whether the serum dioxin levels of individuals living in Calcasieu Parish (including Mossville) were elevated compared to the serum levels of individuals living in Lafayette Parish, where no dioxin releases had occurred.

This study demonstrated that despite the known releases of dioxins to the environment in Calcasieu Parish, the level of uptake and accumulation among that population did not differ from the levels demonstrated in the general United States population or residents of Lafayette Parish, which had no known releases of dioxins. Overall, mean serum dioxin levels did not differ between the study and comparison group, and serum levels were similar for the Calcasieu residents regardless of the distance of their homes from the industrial area, whether they ate fish, smoked, used pesticides or had occupational exposure to dioxin. Dioxin levels increased with age in both Calcasieu and Lafayette Parishes but blood dioxin levels were about half the national average among the youngest age group evaluated (ages 15 to 29). ATSDR concluded that there were no unusual current dioxin exposures occurring for people in those parishes and that the elevated blood dioxin levels in older participants were likely from past exposures (ATSDR 2005).

These results were mirrored by a body burden study conducted on a cohort of women from the Kanawha River Valley in West Virginia (Dilberto et al. 2008). This area had a history of extensive industrial activities, and dioxins and furans have often been represented as a substantial fraction of the overall potential risk to human and ecological receptors that have previously been evaluated there. Because it was known

that dioxins were still present in soil, sediment, groundwater and surface water in portions of this area, thirty years after production of 2,4,5-trichlorophenoxyacetic acid was terminated, a cohort of women who were expected to have higher levels of exposure than the general United States population were selected for evaluation. Blood samples were collected from the Kanawha River Valley cohort and analyzed for seven dioxin congeners, 210 furan congeners and 46 PCB congeners. Total serum concentrations were reported for all of these compounds using the WHO TEQ system that was in place in 2005. These blood levels were then compared with blood concentrations reported in the NHANES data provided in the 2001 report.

The results of this study demonstrated that the serum levels of dioxin-like compounds in this group of women were similar to the serum levels reported in the NHANES data. For the 20 to 39 year old age group, NHANES reported 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentiles of TCDD-TEQ to be 6.6, 10 and 13.7 ppt lipid, respectively, while the same percentile levels measured in the West Virginia cohort were very similar at 6.61, 10.47 and 12.36 ppt lipid, respectively. The same similarities were noted in the 40 to 46 year old age group. The authors concluded that living in this area, which was known to have elevated environmental levels of dioxins, did not result in elevated serum concentrations of those compounds.

In summary, nine studies have been cited demonstrating that soil ingestion is at most an extremely minor exposure pathway for the U.S. population. The data in this section also indicate that direct contact exposure to contaminated soils does not contribute substantially to body burdens. ARCADIS is unaware of any studies reaching contrary conclusions. Even when there is known potential for exposure to elevated concentrations of dioxin in soils to occur, actual uptake does not appear to correlate with soil levels. Evaluation and acknowledgement of the very limited contribution of direct contact with soil on total exposure to TCDD-TEQ is important because even if all of the TCDD-TEQ were eliminated from direct contact soil areas, background concentrations would remain largely the same, due to the fact that the primary source of exposure, food ingestion, would not change. As a result, a reduction in soil target cleanup levels would have essentially no impact on potential exposures and risks due to dioxins and furans in the environment and no meaningful public health benefit.

**Comment 5: EPA is committed to using the “best available science” in its decision making, but the newly proposed OSF and RfD do not consider, and are not based upon, the best available science.**

The EPA has repeatedly and publicly proclaimed its commitment to using the “best available science” in all of its actions. During Lisa Jackson’s confirmation hearing on January 14, 2009, Ms. Jackson stated:

"The environmental and public-health laws Congress has enacted direct the EPA administrator to base decisions on the best available science. EPA's addressing of scientific decisions should reflect the expert judgment of the Agency's career scientists and independent advisors."

"If I am confirmed, I will administer with science as my guide. I understand that the laws leave room for policy-makers to make policy judgments. But if I am confirmed, political appointees will not compromise the integrity of EPA's technical experts to advance particular regulatory outcomes."

In addition, the President has directed the federal agencies, including the EPA, to use the *best available science*. On March 9, 2009, President Obama issued a *Memorandum for the Heads of Executive Departments and Agencies* on the subject of Scientific Integrity. In this memorandum, the President directed the following:

"Specifically, I direct the following:

1. Within 120 days from the date of this memorandum, the Director shall develop recommendations for Presidential action designed to guarantee scientific integrity throughout the executive branch, based on the following principles:

(a) The selection and retention of candidates for science and technology positions in the executive branch should be based on the candidate's knowledge, credentials, experience, and integrity;

(b) Each agency should have appropriate rules and procedures to ensure the integrity of the scientific process within the agency;

(c) When scientific or technological information is considered in policy decisions, the information should be subject to well-established scientific processes, including peer review where appropriate, and each agency should appropriately and accurately reflect that information in complying with and applying relevant statutory standards;"

On May 9, 2009, EPA's Administrator, Lisa Jackson, issued a memorandum to all EPA employees on the subject of Scientific Integrity: *Our Compass for Environmental Protection*. In that memorandum, Ms. Jackson stated:

"On March 9, President Obama issued a Memorandum on Scientific Integrity underscoring that the "public must be able to trust the science and scientific

process informing public policy decisions.” The public health and environmental laws that Congress has enacted depend on rigorous adherence to the best available science. That is why, when I became Administrator, I pledged to uphold values of scientific integrity every day.”

Clearly, EPA, as required by President Obama, has promised to take actions after considering and acting upon the “*best available science*.” The commitment to use the best available science is not really new as of 2009. In 2003, EPA, Office of Solid Waste and Emergency Response (OSWER), issued OSWER Directive 9285.7-53, which was entitled *Human Health Toxicity Values in Superfund Risk Assessments* (EPA 2003b). In this directive, EPA committed to using the best available science in deriving toxicity values for use in Human Health Risk Assessment (HHRA). The directive specifically states:

“This revised hierarchy recognizes that EPA should use the best science available on which to base risk assessments.

In conclusion, EPA has stated its general intent to rely on the “*best available science*.” With regard specifically to the proposed OSF and RfD, ARCADIS offers many comments below that demonstrate that EPA has not even *considered*, much less *used*, the “*best available science*” in deriving the proposed OSF and RfD.

## SPECIFIC TECHNICAL COMMENTS

### A. COMMENTS ON THE PROPOSED ORAL CANCER SLOPE FACTOR

#### **Comment 6: EPA's evaluation of 2,3,7,8-TCDD as "carcinogenic in humans" is inconsistent with the 2005 cancer guidelines.**

In the NAS Review Draft, EPA (2003a) proposed a weight of evidence classification of "carcinogenic in humans" for TCDD. In their review of the NAS Review Draft, the NAS (2006) did not reach consensus on EPA's (2003a) proposed classification of TCDD as carcinogenic to humans. Their primary concern was how EPA would interpret and apply condition (a) of the EPA (2005) *Guidelines for Carcinogen Risk Assessment*, which states "there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association". The NAS (2006) agreed with EPA (2003a) that correlations between dioxin exposure and mortality from all cancer was positive, but not strong, and that associations between exposure and any specific tumor type was limited. The NAS (2006) also agreed with EPA (2003a) that "there is convincing evidence supporting the interaction of dioxin with the human Ah receptor (AhR) and that the interaction with the receptor was necessary, but not sufficient, to cause cancer in animals. However, the committee was not in complete agreement about whether these conditions met the stated criterion of a 'key precursor event of the agent's mode of action'."

To further evaluate how EPA (2010a) addressed NAS (2006) comments on this issue it is important to be clear about the EPA (2005) definition of "carcinogenic to humans". According to EPA (2005),

"This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.
- Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when all of the following conditions are met:
  - (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and

- (b) there is extensive evidence of carcinogenicity in animals, and
- (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and
- (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on mode of action and also an indication of the relative weight that each source of information carries, e.g., based on human information, based on limited human and extensive animal experiments.”

These descriptors have not been used by EPA as noted below.

**Comment 7: The epidemiology studies alone do not support the inference of causality.**

Clearly, the NAS (2006) did not agree that there was strong evidence of carcinogenicity in humans based on epidemiology studies. Thus, following the 2005 cancer guidelines, each of the remaining four criteria (a through d) must be met for classifying TCDD as “carcinogenic in humans”.

In their Reanalysis, EPA (2010a) evaluated the epidemiological evidence in the context of six Hill Criteria (temporality, strength of association, consistency, biological plausibility, biological gradient, and specificity). They concluded that “the available epidemiological information provides strong evidence of an association between TCDD exposure and human cancer that cannot be reasonably attributed to chance or confounding and other types of bias, and with a demonstration of temporality, strength of association, consistency, biological plausibility, and a biological gradient.”

Regarding **temporality**, there is no question that if the increased mortality observed in the Seveso and occupational cohorts is due to chemical exposure, then that latency time between exposure and mortality meets the criterion of temporality.

On **strength of association**, NAS (2006) concluded that the correlations between TCDD exposure and mortality are not strong. This conclusion is sound given the low statistical power of many of the studies, the lack of consistency and specificity in tumor types across studies, and the fact that many of the risk ratios (RRs) reported were

borderline statistically significant with RRs often inclusive of unity. In their evaluation of strength of association, EPA (2010a) *assumed* that TCDD was the causative agent and did not consider exposures to other chemicals by occupational workers and Seveso residents, including other dioxin-like chemicals (DLCs), which were not controlled for in the epidemiology studies, nor did they adequately consider the uncertainty in the exposure estimates that in turn may increase or decrease the magnitude of the reported RRs as well as their statistical significance.

For the **consistency** criterion, EPA (2010a) acknowledged that tumor types were not consistent across studies, but that there was consistency with increased mortality associated with all cancers. EPA (2010a) states that, "the observation of the same site-specific effect across several independent study populations strengthens an inference of causality." Mortality associated with all cancers is not a valid metric for evaluating consistency, and the observation of increased mortality from all cancers across studies does not strengthen the inference of causality. Rather, a lack of similar site-specific effects across all studies (including negative studies not considered by EPA) weakens the inference of causality.

In their evaluation of **biological gradient**, EPA (2010a) indicates that several of the studies of occupational cohorts found evidence of a dose response relationship for all cancers and various TCDD exposure measures, and that a dose-response relationship was observed for breast cancers and TCDD exposure in the Seveso population. However, EPA (2010a) failed to balance these findings with the negative findings from TCDD epidemiology studies that did not observe a dose-response relationship between cancer mortality and TCDD exposure. As noted previously, EPA (2010a) also did not consider other chemical exposures experienced by these cohorts.

Consistent with the NAS (2006) comments regarding AhR mediation and key precursor events, EPA's argument on **biological plausibility** is almost entirely focused on AhR activation. Specifically, the NAS (2006) noted that, "The committee agreed that there is convincing evidence supporting the interaction of dioxin with the human Ah receptor and that the interaction with the receptor was necessary, but not sufficient, to cause cancer in animals. However, the committee was not in complete agreement about whether these conditions met the stated criterion of a "key precursor event of the agent's mode of action". For example, it was noted that, even though TCDD binds to the human Ah receptor, several endogenous and exogenous substances, including bilirubin, biliverdin, and  $\beta$ -naphthoflavone, also bind to the Ah receptor but are not carcinogenic in rodent models (Seidel et al. 2000); hence, some other key precursor event(s) may need to be identified to meet that criterion." EPA (2010a) has clearly not adequately addressed this NAS (2006) comment as it related to the evaluation of causality.

EPA (2010a) states that under the current 2005 cancer guidelines, the absence of **specificity** does not detract from the evidence of causality, but when present would support an inference of causality. However, it appears that EPA (2010a) argues that AhR activation across species is relevant to the evaluation of specificity. In this context, AhR activation alone is not sufficient to elicit a carcinogenic response, and therefore, is not relevant to the issue of specificity as it relates to carcinogenic response. As noted by NAS (2006), AhR activation occurs not only with TCDD and other DLCs but also with agents that do not elicit a carcinogenic response. Clearly, specificity in the tumor types observed across multiple TCDD epidemiology studies is marginal at best. NAS (2006) concluded that specificity in tumor types across the various epidemiology studies was limited.

In the following table, the individual causal criteria as they relate to TCDD exposure and its possible association with cancer as reported in the epidemiology studies are summarized.

**TABLE 8  
SUMMARY OF CAUSAL CRITERIA**

<b>Criteria for Inferring Causation</b>	<b>Strength of Causal Evidence</b>
Temporality	Strong – In most cohorts, increased mortality was observed following a sufficient period of latency following exposure.
Strength of Association	Weak – magnitude of risk estimates (e.g., RRs) were small and statistical significance was often marginal. Confounding by other chemical exposures not accounted for. Uncertain measures of exposure in many studies.
Consistency	Moderate – with respect to mortality associated with all cancers; however, this does not include an adequate balance between positive and negative studies. Evidence for specific tumor types is weak.
Biological Plausibility	Moderate – AhR mediation and evidence that TCDD is carcinogenic in laboratory animals is strong, but evidence regarding key precursor events is weak. AhR mediation is necessary but not sufficient to cause cancer.
Biological Gradient	Weak – dose response relationships are compromised by uncertain estimates of exposure, a limited number of exposure groups, usually ranging from one to three, and oftentimes the absence of a reference group.

Criteria for Inferring Causation	Strength of Causal Evidence
Specificity	Weak – Different tumor types have been observed much more frequently across studies, than similar tumor types.

Consistent with the conclusions reached by the NAS (2006), it is concluded that based only on the epidemiology studies, the evidence for causation by TCDD is weak to moderate and clearly not the strong evidence of causation as EPA (2010a) purports it to be. While the limitations in strength of association, consistency, biological gradient, and specificity are clearly the criteria that most significantly detract from the inference of causation, the single most important limitation is the failure of nearly all studies to quantitatively (or qualitatively for that matter) account for the confounding effects of the other chemical exposures, including other DLCs. In the absence of this understanding, it can only be concluded that TCDD may be a reasonable marker of exposure as it may relate to certain health outcomes.

In the absence of strong evidence of causality directly from the epidemiology studies, EPA (2005) provided additional criteria that can infer causality, but causality can be demonstrated only if *all* of these criteria are met. These were summarized above and are discussed below.

**Comment 8: Other lines of evidence specified in the EPA cancer guidelines do not support the inference of causality.**

There is clearly strong evidence that TCDD is carcinogenic in laboratory animals. As discussed above, the evidence from epidemiology studies is weak to moderate, but is certainly not *strong* evidence. In the absence of these criteria, the weight of evidence relies primarily on whether there is an adequate understanding of key precursor events to suggest that such events would lead to a carcinogenic response in humans. EPA (2010a) focused largely on AhR activation as key precursor event.

In their concluding paragraph discussing TCDD's mechanism of action, EPA (2003a) states:

“Thus, at present the wealth of evidence available indicates that most, if not all, of the biological and toxic effects of dioxins are mediated by the Ah receptor. Although the receptor may be necessary for the occurrence of these events, clearly it is not sufficient because other proteins and conditions are known to affect activity of the receptor and its ability to alter gene expression. There is some evidence to support mechanisms involving pathways for Ah receptor action that do not

involve Arnt, although the exact steps involved in these pathways have yet to be fully detailed.”

Obviously, EPA (2003a) agrees the key precursor events leading from AhR activation to a carcinogenic response have not been fully elucidated. AhR activation is most likely required. But as NAS (2006) noted, AhR activation alone is not sufficient to describe the mode of action by which TCDD may cause cancer in humans. In the absence of more clear understanding of the mode of action by which TCDD may cause cancer in humans, it can only be concluded that the EPA (2005) criteria related to key precursors has not been met. In their Reanalysis, EPA (2010a) states that, “While the mode of action of TCDD in producing cancer has not been elucidated for any tumor type, the best characterized carcinogenic actions of TCDD are in rodent liver, lung, and thyroid.” In the subsequent tumor-specific chapters, EPA (2010a) then states,

- “The mode of action of TCDD in producing liver cancer in rodents has not been elucidated.”
- “The mode of action of TCDD in producing lung cancer in rodents (predominantly keratinizing squamous cell carcinoma), has not been elucidated.”
- “The mode of action of TCDD in producing thyroid cancer in rodents has not been elucidated.”

Thus, by EPA's (2010a) own admission, the key precursor events leading to a carcinogenic response by TCDD are not fully understood. While EPA (2010a) attempted to address the NAS (2006) comments on this issue, they have not provided any additional evidence to alleviate the NAS committee's concern regarding the EPA (2005) criteria for causation as it relates to key precursor events.

In summary, neither the epidemiology studies themselves nor the additional lines of evidence outlined by EPA (2005) are sufficient to support the classification of TCDD as “carcinogenic to humans” although the evidence appears to support the classification of TCDD as “likely carcinogenic to humans”, a determination that appears to be largely supported by the NAS (2006). When considering whether TCDD is a causative agent in the epidemiology studies, the greatest concern is the lack of control for the very likely confounding effect of other chemical exposures in both the occupational cohorts and the Seveso population. This issue is discussed in more detail elsewhere in these comments.

**Comment 9: The issue of causality in the TCDD epidemiology studies directly affects the use of these studies for conducting cancer dose response assessments.**

In their Reanalysis, EPA (2010a) has proposed an oral cancer slope factor (OSF) of  $1 \times 10^{-6}$  based on a study by Cheng et al. (2006). The Cheng et al. (2006) study is among the more recent re-evaluations of the NIOSH cohort of 5,172 U.S. workers employed on average for 12.6 years at one of 12 different chemicals plants. While Cheng et al. (2006) clearly provides the most robust dose response analysis of this cohort, there are two significant concerns.

- First, is it valid to even attempt a dose-response assessment using epidemiological data when a causal association between TCDD exposure and cancer has not been demonstrated in these studies?
- Second, what is the relevance of a dose-response analysis using only TCDD exposure as the dose metric when in fact these U.S. workers were exposed to many chemicals in the workplace, including other DLCs as well as non-DLCs that may be carcinogenic?

When conducting dose-response assessments on tumor incidence in laboratory animal studies, it is usually done for those tumor incidences that are shown to be statistically significant and demonstrate a dose-response relationship (increased incidence corresponding to increased dose). These two factors demonstrate that the dosing agent "caused" a carcinogenic response. By analogy, when evaluating epidemiology data for the purpose of evaluating dose response, it seems prudent to first ask the question whether the agent in question "caused" the reported health outcome. In the case of TCDD and increased cancer mortality as reported in the occupational studies and in the Seveso studies, there is insufficient evidence to conclude that TCDD is the causative agent, which has been discussed in more detail elsewhere in these comments.

Equally, if not more important, is the approach of dose-response modeling of TCDD in the NIOSH cohort when it is known that these workers were exposed to other DLCs, and very likely other carcinogens. At best, using only TCDD as a measure of exposure will substantially underestimate the dose and consequently overestimate the OSF.

As stated by EPA (2010a), in regards to the NIOSH study,

"Workers in this cohort also were exposed to other chemicals, which could lead to bias due to confounding if these exposures were

associated with both TCDD exposure and the health outcomes being examined. At one plant, workers were exposed to 4-aminobiphenyl. Previous investigators also reported that workers at another plant were exposed to 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) (Bond et al., 1988, Bond et al., 1989, Ott et al., 1987). Although this study did not examine the impact of confounding by other occupational coexposures, subsequent analyses of this cohort showed that associations between cumulative TCDD and all cancer mortality persisted after excluding workers exposed to pentachlorophenols from the analyses (Steenland et al., 1999). Removal of workers who died from bladder cancer also did not substantially change the dose-response association between TCDD and cancer mortality from all other sites combined. This finding suggests that exposures to 4-aminobiphenyl did not confound the association between cancer mortality and TCDD exposure. Overall, there is little evidence of confounding by these co-exposures among this cohort, however, exposure to other possible confounders, such as dioxin-like compounds, was not examined.”

Consideration of these questions requires a close look at the Cheng et al. (2006) study. Cheng et al. (2006) presented standardized mortality rates (SMRs) separately for each of 10 chemical plants for all cancers, lung cancer, smoking-related cancers, all other cancers, and non-malignant respiratory disease (NMRD). Of these 10 chemical plants, significantly elevated SMRs ( $p < 0.05$ ) were not observed in 8 of 10 chemical plants for any of these groupings of cancer mortality. At Plant 8, a significantly elevated SMR was reported only for smoking related cancers. At Plant 10 significantly elevated SMRs were observed for all cancers, lung cancer, smoking related cancers, and NRMD, but not for all other cancers (unrelated to smoking). SMRs associated with all other cancers were not significantly elevated at any of the 10 chemical plants nor was the SMR for all other cancers significantly elevated when data from all 10 plants were combined.

In their SMR analysis, Cheng et al. (2006) noted that in comparison to the general population, the study group had 17% increase in mortality from all cancers, a 22% increase in mortality from smoking related cancers, and a 12% increase in mortality from all other cancers. As noted above, the increased mortality associated all other cancers was not statistically significant.

While the Cox regression analysis performed by Cheng et al. (2006) found a similar association of TCDD exposure and smoking-related cancer mortality and mortality from all other cancers, this finding is not unexpected when TCDD is viewed as a marker of

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exposure. Given its persistence and high bioaccumulative potential, a strong relationship between TCDD serum concentrations and exposure duration would be anticipated as well as a strong relationship between TCDD serum concentrations and health outcomes since the elevated SMRs are directly related to the overall long term exposure experience and lag time. Of particular interest is the absence of statistically significant elevated SMRs for mortality-associated cancers other than those related to smoking, and the absence of any significantly elevated SMRs in workers from 8 of 10 plants. One would expect that if TCDD was the causative agent for increased cancer mortality, one would see a consistent pattern across all chemical plants.

Plant 10 is clearly unique among the 10 chemical plants evaluated by Cheng et al. (2006), showing significantly elevated SMRs for all cancers, lung cancer, other smoking related cancers, and NMRD. Given the magnitude of the SMRs for each of the individual chemical plants relative to the SMRs for Plant 10, it is likely that if Plant 10 was excluded from the SMR analysis, then the overall SMRs for all chemical plants (excluding Plant 10) would not be significantly elevated. Because workers from all 10 chemical plants experienced exposure to TCDD, yet plant-specific SMRs do not suggest a common risk factor, it stands that other chemical exposure or other risk factors should be evaluated at each chemical plant (particularly Plant 10) in effort to more thoroughly evaluate the possible causal relationships between TCDD exposure and other risk factors to increased mortality (again, particularly for Plant 10). Exposure to other chemicals has been described for some of these chemical plants (e.g., 4-aminobiphenyl at Plant 8, 2,4,5-T, 2,4-D, & pentachlorophenol), but not in a comprehensive manner that would allow a thorough examination of their possible relationships to cancer mortality.

In the absence of a more thorough evaluation of other risk factors, it cannot be concluded that TCDD was the causative agent related to cancer mortality in these U.S. chemical plant workers. If TCDD is not the causative agent related to cancer mortality in this cohort, and TCDD is merely a very good marker of exposure, then it becomes critically important to question the meaningfulness of any TCDD dose-response modeling based on cancer mortality of U.S. occupational workers.

**Comment 10: The proposed OSF is based on extremely weak epidemiological evidence: marginally statistically significant increases in larynx and bladder cancer at only two of the eight workplaces.**

Cheng et al. (2006) reported statistically significant increases in all cancer mortality, combined from eight workplaces. However, the statistical significance is marginal. The 95% confidence interval on the Standardized Mortality Ratio was 103-132, barely over

100. Based on data in Table II, it is clear that total cancer mortality was statistically significantly increased in only one of the eight workplaces.

These increases were dominated by Smoking Related Cancers, including oral cavity/pharynx, esophagus, larynx, lung and bladder. Again, the statistical significance was very marginal. In this case, the 95% confidence interval on the Standardized Mortality Ratio (SMR) was 101-145. Findings associated with such marginal SMR increases of this magnitude can only be considered as hypothesis-generating because they are likely be the result of a spurious association between exposure and cancer outcome. In this case, the increases were *not* statistically significantly increased in six of the eight workplaces. According to the authors, "The excess of smoking-related cancer was due to excesses of larynx and bladder cancers, in addition to cancer of the lung." However, the overall statistics for lung cancer were not statistically significantly increased with the 95% confidence interval on the Standardized Mortality Ratio of 89-137. Thus, the result of Cheng et al. (2006) that was used by EPA to derive the proposed OSF for dioxin were due to increased mortality in two workplaces to two cancer sites that are highly associated with smoking: larynx and bladder.

This data set is weak and it presents results allegedly associated with dioxin exposure that have not been seen in other studies of workers exposed to dioxin and dioxin-like compounds. In addition, these cancers were not elevated in a 20-year follow-up of the population surrounding Seveso, Italy explosion in 1976 (Pestori et al. 2009).

Furthermore, Cheng et al. (2006) stated that the total cancers were skewed by bladder cancers at Plant 8, that were not associated with dioxin exposure, but rather "attributed to exposure to 4-aminobiphenyl..." More importantly, smoking is a very likely confounding exposure for "smoking related cancers" as noted by Cheng et al. (2006): "The elevations in deaths from nonmalignant respiratory disease in Plants 8 and 10 suggest that smoking may have contributed to the observed excess lung and total cancer mortality at these plants. However, we do not know if smoking confounded the dose-response relation between TCDD and cancer mortality, or if so, the net direction of such confounding."

**Comment 11: The proposed Oral Cancer Slope Factor (OSF) of 1,000,000 (mg/kg-day)<sup>-1</sup> does not represent the "best available science," because it is highly uncertain.**

Cheng et al. (2006) report risk estimates for a 5 ppt serum level in Table IV that range from  $6.3 \times 10^{-7}$  to  $7.0 \times 10^{-4}$ . This range of uncertainty is three orders of magnitude! The authors understand this uncertainty and discuss it as follows:

"...a range of estimated risks spanning more than two orders of magnitude can be obtained using various plausible assumptions. This uncertainty does not include the additional contributions from interindividual differences in elimination kinetics, uncertainties due to uncontrolled confounding, or the additional variability that could be expected from inclusion of data from other occupational cohorts. Such variability and uncertainty needs to be acknowledged when quantitative assessments of potential human cancer risks at background exposure levels are conducted."

The risk estimates are too uncertain for EPA to use them to derive an OSF.

**Comment 12: The proposed Oral Cancer Slope Factor (OSF) of 1,000,000 (mg/kg-day)<sup>-1</sup> does not represent the "best available science," because it is inconsistent with the current state of the science on TCDD's potential carcinogenicity.**

The proposed OSF of 1,000,000 (mg/kg-day)<sup>-1</sup> is not a scientifically sound cancer-based toxicity benchmark for TCDD for numerous reasons:

1. The OSF is based on a study that was only marginally statistically significant for total cancer mortality and two sites: bladder cancer and larynx cancer.
2. Total cancer, bladder cancer and larynx cancer were not elevated in a 20-year follow-up study of residents of Zones A, B, and R surrounding the Seveso, Italy dioxin explosion in 1976.
3. Its derivation using a linear dose-response model is inconsistent with TCDD's mode of action.
4. The doses to all decedents and cancer decedents are equivalent.

The following discussions on the selection of an appropriate OSF are prefaced with the understanding that the OSF approach for describing the carcinogenic potency of TCDD and related compounds is not valid based on their non-linear threshold mode of action.

There are a number of additional OSFs that EPA should also have considered including those derived by the U.S. Food and Drug Administration (FDA) and those that have been published in the peer-reviewed scientific literature, as summarized below:

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- Keenan et al. (1991) – OSF of 9,700 (mg/kg-day)<sup>-1</sup> published in the peer-reviewed literature and based on re-evaluation of the Kociba pathology slides.
- FDA (1993) – OSF of 9,000 (mg/kg-day)<sup>-1</sup> based on re-evaluation of the Kociba pathology slides.
- FDA (1994) – Revised OSF of 30,000 (mg/kg-day)<sup>-1</sup> based on re-evaluation of the Kociba pathology slides and revised consensus cross-species scaling factor.
- Crouch (2005) – Median OSF of 7,000 (mg/kg-day)<sup>-1</sup> and upper-bound OSF of 52,900 (mg/kg-day)<sup>-1</sup> based on the probability density function of the OSF from combining 10 cancer bioassays.
- Maruyama and Aoki (2006) – Best estimate OSF of 1,600 (mg/kg-day)<sup>-1</sup> and an upper-bound OSF of 3,000 (mg/kg-day)<sup>-1</sup> based on toxicokinetic modeling of National Toxicology Program (NTP 2006) rat liver tumor results and linear benchmark dose-response modeling.
- Office of Environmental Health Hazard Assessment (OEHHA 2007) – OSF of 26,300 (mg/kg-day)<sup>-1</sup> based on recent NTP (2006) two-year rat bioassay and Monte Carlo simulations to sum OSFs across multiple tumor sites.
- Simon et al. (2009) – OSF of 100,000 (mg/kg-day)<sup>-1</sup> based on the recent NTP (2006) 2-year rat bioassay, toxicokinetic modeling to estimate lifetime average liver TCDD concentrations in rats, benchmark dose-response modeling, toxicokinetic modeling to estimate human equivalent dose, and estimation of the linear OSF.

The implications of the most current science and regulatory guidelines and policies, as they relate to carcinogen dose-response of TCDD, are discussed below.

#### Consideration of EPA (2005) Cancer Risk Assessment Guidelines and Other Very Recent Information

In 2005, the EPA published its final *Guidelines for Carcinogen Risk Assessment*. In contrast to the default standard practice in 1985 of assuming a non-threshold linear dose response, the 2005 guidelines provide alternative methods for conducting dose-response modeling that incorporate information on mode of action, pharmacokinetics, and non-linear dose-response relationships. Importantly, EPA (2005) does not view the selection of a default OSF as trivial:

“Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information. “

Since 1991, the EPA has expended considerable effort on evaluating the toxicity of TCDD and related compounds through the Dioxin Reassessment process. Their 2003 Dioxin Reassessment Report and subsequent critical review by the NAS in 2006 have demonstrated that EPA has sufficient and reliable information from which to derive a scientifically sound animal-based human OSF following the 2005 cancer risk assessment guidelines.

Mode of action is the primary focus of the 2005 cancer risk assessment guidelines. EPA (2005) emphasized the importance of including mode of action in dose-response assessment, including during the selection of the most appropriate dose-response model.

EPA (2005) recommended that linear models should be used when agents are DNA-reactive and have direct mutagenic activity and when human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process. Numerous studies have shown that TCDD is not DNA-reactive and has little mutagenic activity. Environmental exposure (doses and body burdens) to TCDD and related compounds is extremely low in the general United States population, and substantially lower than historical occupational exposures that might have suggested exposures and body burdens possibly corresponding to the doses associated with key precursor events.

Conversely, EPA (2005) recommends that non-linear models should be used when there are sufficient data to ascertain the mode of action, demonstrate that the dose-response is not linear at low doses, and that the agent is not mutagenic. Both the EPA (2003a) and the NAS (2006) agreed that TCDD is not an initiator, but is, rather, a promoter in the carcinogenesis process. On the issue of low dose linearity, the NAS (2006) concluded that:

“...although it is not possible to scientifically prove the absence of linearity at low doses, the scientific evidence, based largely on mode of action, is adequate to favor the use of a nonlinear model that would include a threshold response over the use of the default linear assumption.”

The NAS (2006) drew this conclusion on the basis of four factors.

- TCDD and related compounds are not directly genotoxic;
- Receptor-mediated agents have sublinear dose-response relationships;
- Liver tumors are secondary to hepatotoxicity, suggesting a cytotoxic mechanism through cell proliferation; and
- There is bioassay evidence of non-linearity.

Based on the conclusions of the NAS regarding TCDD's mode of action, the application of linear non-threshold models for TCDD is no longer justified. More importantly, the OSF methodology for characterizing TCDD cancer potency is clearly not valid as it inherently assumes non-threshold response. That is, it assumes some probability of a carcinogenic response at any dose. To date, Simon et al. (2009) is the only published study that fully integrates EPA's (2005) carcinogen dose-response guidance with the most current cancer bioassay data. Using the NTP (2006) bioassay, Simon et al. (2009) derived a cancer-based RfD of 100 pg/kg-day using benchmark modeling and application of uncertainty factors, consistent with EPA (2005) guidance. This approach most accurately reflects TCDD's mode of action and is consistent with the recommendation of the NAS (2006).

By deriving an OSF of  $1,000,000 \text{ (mg/kg-day)}^{-1}$ , derived using a non-threshold linear model, the EPA has ignored the current state of the science regarding the carcinogenic dose-response of TCDD. These very same views that the NAS (2006) provided to the EPA have been expounded for over two decades by the scientific community in peer-reviewed publications, yet EPA continues to ignore the scientific evidence.

**Comment 13: The proposed OSF is inconsistent with background levels of dioxin-like compounds in soils nationwide and is thus unreasonable. EPA should not establish an OSF that results in soil cleanup levels that are below typical background levels in soil.**

When EPA proposed both cancer- and noncancer-based PRGs for residential and commercial/industrial soils, EPA (2009a) recommended the interim PRGs for soil that were calculated based on noncancer effects: 72 ppt TCDD-TEQ in residential soil and 950 ppt TCDD-TEQ in commercial/industrial soil. They further stated that they believed that these recommended PRGs generally provide adequate protection against noncancer effects and cancer effects at the  $1 \times 10^{-5}$  risk level. However, EPA then went on to say that they were also considering an alternative concentration of 3.7 ppt TCDD-TEQ in residential soil and 17 ppt TCDD-TEQ in commercial/industrial soil; these are cancer-based PRGs derived by EPA at the  $1 \times 10^{-6}$  risk level. EPA further states that

these cancer-based PRGs at the  $1 \times 10^{-6}$  risk level are within or possibly below background concentrations of dioxins in United States soils. EPA cited, as support, a recent EPA report that demonstrated mean rural soil TEQ concentrations ranging from 0.2 to 11.4 ppt (EPA 2007).

EPA has not issued the Final Interim PRG yet, but the 3.7 ppt PRG being considered by EPA is based on the currently-used OSF of  $156,000 \text{ (mg/kg-day)}^{-1}$ . This PRG will drop to 0.6 ppt if the proposed OSF of  $1,000,000 \text{ (mg/kg-day)}^{-1}$  is promulgated.

When proposing a new OSF, it is important to consider how that OSF will be used and how it will relate to Regional Screening Levels and target clean up levels for soils. To that end, it is critical that background be adequately characterized, both generically and on a site-specific basis. EPA's characterization of background concentrations of dioxin in United States soils is misleading. For the purpose of comparing risk-based soil concentrations against background concentrations, the reported mean background concentration substantially simplifies and understates the full range of background soil dioxin concentrations to which individuals in the United States are exposed. The EPA (2007) study that EPA (2009a) referenced was a small pilot study with data from only 27 locations across the entire country. EPA (2007) is clear that, "The results presented pertain to the 27 sites sampled and should not be more broadly interpreted as statistically representative of all rural soils in the United States."

The largest background study conducted in the United States was completed by the EPA (Region 8) in 2001 (EPA 2001). A total of 160 soil samples were collected from five different areas near Denver, Colorado, including open space (37 samples), agricultural (27 samples), residential (37 samples), commercial (30 samples) and industrial (29 samples) soils. Mean soil TEQ concentrations for open space, agricultural, residential, commercial and industrial soils were 1.6, 1.6, 7.1, 6.4 and 9.8 ppt, respectively. However, the range of TEQ concentration was quite large, with maximum soil TEQ concentrations for open space, agricultural, residential, commercial, and industrial soils of 9.1, 7.7, 43, 57, and 54 ppt., respectively. These results are consistent with a 1995 study conducted in British Columbia that reported background dioxin TEQ concentrations ranging up to 57 ppt in non-impacted areas (BC Environment 1995).

The two alternative Interim PRGs proposed by EPA in 2009 of 3.7 and 17 ppt TCDD-TEQ, which were derived by EPA based on carcinogenic effects, are well within these ranges of background soil dioxin concentrations. Using the newly proposed OSF, these two values would be revised to 0.6 and 2.6 ppt, the low end of which is clearly below the ranges of background concentrations. An important practical implication of the

proposed OSF is that health-based screening levels and target clean-up levels for soil will be below background in many locations throughout the United States.

**Comment 14: The proposed Interim Preliminary Remediation Goal does not reflect the “best available science,” because EPA did not include probabilistic approaches to characterize variability and uncertainty as recommended by the NAS in their 2006 review of EPA’s dioxin reassessment and in their 2008 *Science and Decisions: Advancing Risk Assessment*.**

The NAS recommended that EPA should include probabilistic assessments in their evaluation of dioxin to aid in the understanding of the variability and uncertainty inherent in the evaluation of exposure to dioxin (NAS 2006). Specifically, NAS (2006) stated:

“describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key end-point-specific risk assessment (choices of data set, POD, model, and dose metric); incorporate probabilistic models to the extent possible to represent the range of plausible values; and assess goodness-of-fit of dose-response models for data sets and provide both upper and lower bounds on central estimates for all statistical estimates.”

The incorporation of a probabilistic evaluation would aid in identifying the uncertainties that drive the risk assessment. It would also allow the risk assessor to identify areas to develop site-specific assumptions which would have the greatest influence on the results of the assessment.

In evaluating the exposure assessment, the NAS (2006) concluded that while “EPA has qualitatively identified a number of important uncertainties and variabilities,” they did not provide a quantitative evaluation of variability or uncertainty in exposure except on a limited basis. Thus, to adequately define the ranges in uncertainty and variability, the use of a probabilistic evaluation of the input parameters should be conducted.

In *Science and Decisions: Advancing Risk Assessment* (NAS 2008), NAS called for assessments of uncertainty and variability in all EPA risk assessments, as noted below:

“Recommended Principles for Uncertainty and Variability Analysis

1. Risk assessments should provide a quantitative, or at least qualitative, description of uncertainty and variability consistent with available data. The

information required to conduct detailed uncertainty analyses may not be available in many situations.

2. In addition to characterizing the full population at risk, attention should be directed to vulnerable individuals and subpopulations that may be particularly susceptible or more highly exposed.
3. The depth, extent, and detail of the uncertainty and variability analyses should be commensurate with the importance and nature of the decisions to be informed by the risk assessment and with what is valued in a decision. This may best be achieved by early engagement of assessors, managers, and stakeholders in the nature and objectives of the risk assessment and terms of reference (which must be clearly defined).
4. The risk assessment should compile or otherwise characterize the types, sources, extent, and magnitude of variability and substantial uncertainties associated with the assessment. To the extent feasible, there should be homologous treatment of uncertainties among the different components of a risk assessment and among different policy options being compared.
5. To maximize public understanding of and participation in risk-related decision-making, a risk assessment should explain the basis and results of the uncertainty analysis with sufficient clarity to be understood by the public and decision-makers. The uncertainty assessment should not be a significant source of delay in the release of an assessment.
6. Uncertainty and variability should be kept conceptually separate in the risk assessment."

EPA did not perform probabilistic risk assessment analyses as strongly recommended by the NAS in 2006.

**B. COMMENTS ON THE PROPOSED REFERENCE DOSE****COMMENTS ON MOCARELLI ET AL. (2008)**

**Comment 15: The Reference Dose derived from Mocarelli et al. (2008) does not reflect the “best available science” because it uses the outdated Lowest Observed Adverse Effect Level approach rather than the Benchmark Dose approach which defines current EPA policy.**

EPA currently derives Reference Doses (RfDs) by the use of the Benchmark Dose approach wherein its Benchmark Dose Software (BMDS) is employed to derive a benchmark dose – low (BMDL) for the adverse effect of interest (EPA 2000d). According to EPA's website for BMDS (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=164443>), EPA's policy to use the BMD method dates back to 1995:

“Prior to the 1990's, RfDs and RfCs had been determined from no-observed-adverse-effect levels (NOAELs), which represent the highest experimental dose for which no statistically significant adverse health effects were reported or, in the absence of a NOAEL, the lowest-observed-adverse-effect levels (LOAEL). In 1995, EPA's Risk Assessment Forum published guidance on the benchmark dose (BMD) approach in the assessment of noncancer health risk (U.S. EPA, 1995) which listed several advantages of the BMD approach over use of NOAELs and LOAELs. In 1995, EPA's National Center for Environmental Assessment (NCEA) initiated a project to develop benchmark dose software to assist Agency risk assessors in deriving benchmark dose values for use in Agency risk assessments.”

In this case, EPA should have acquired the raw data from Dr. Mocarelli and determined the BMDL<sub>10</sub> for a specified decrease in sperm concentration in the young men. By failing to use the BMD approach and, instead, defining the median of the first quartile as a Lowest Observed Adverse Effect Level (LOAEL), EPA has bypassed the “best available science,” which EPA has committed to using.

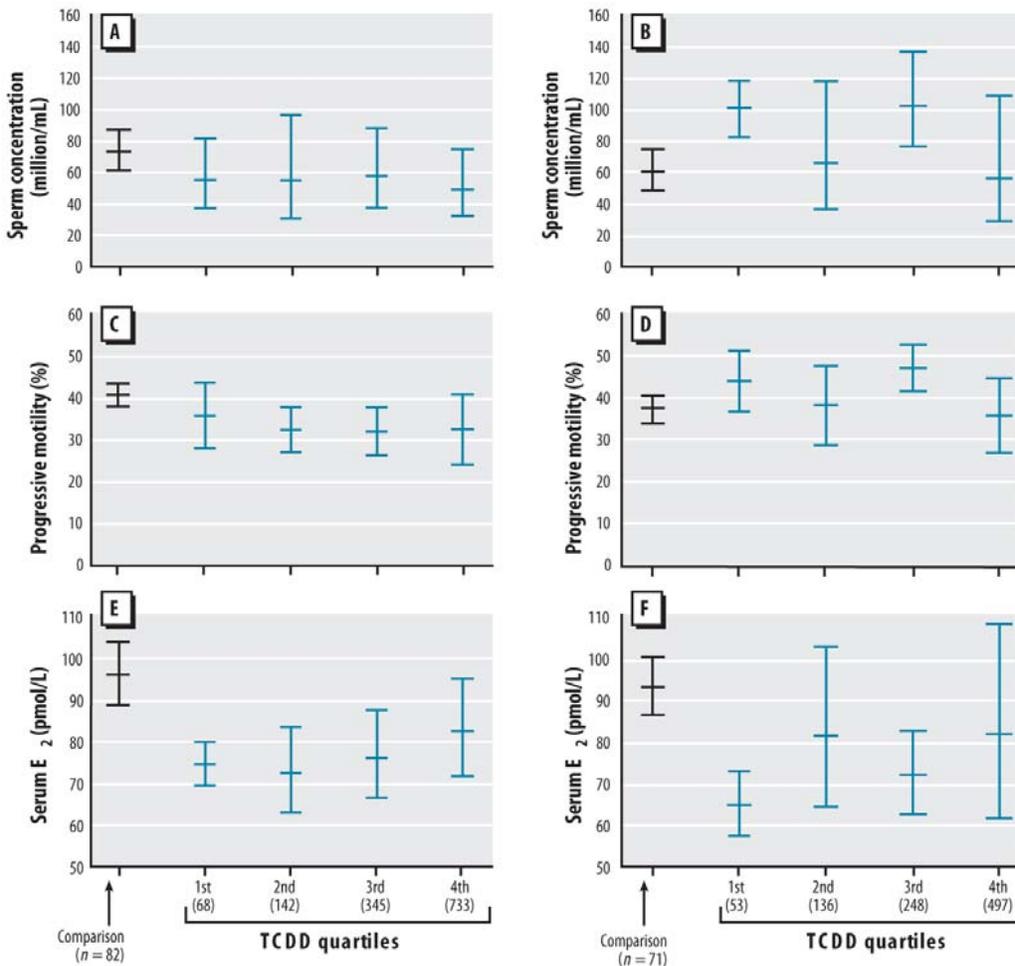
EPA (2010a) does not explain why they did not pursue benchmark dose modeling. EPA states merely that “modeling of a benchmark dose lower confidence bound [BMDL] was not possible given the data presented in these studies.”

**Comment 16: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because it assumes the median of the first quartile from Figure 3 is a LOAEL for a 20% decrease in sperm concentration without any statistical significance testing.**

Mocarelli et al. (2008) found a statistically significant difference between the control group and the men exposed to dioxin as 1-9 year old boys. The mean dioxin exposure of these 71 young boys was 210 ppt and the decrease in sperm concentration found to be significant was a 28% decrease. Neither Mocarelli et al. (2008) nor EPA has performed statistical significance testing to determine if the 20% decrease in sperm concentration when the 18 boys in the first quartile were compared to the control group of 82 unexposed boys.

A casual examination of Figure 3 in Mocarelli et al. (2008) shows that the variability in the sperm concentrations in the comparison group and the four quartile groups is extremely large. It is not at all clear that the effects seen in the first quartile group are statistically significantly different from the comparison group.

FIGURE 11  
FIGURE 3 FROM MOCARELLI ET AL. (2008)



TCDD quartile distribution (adjusted mean and 95% confidence interval) of sperm concentration (A, B), total motile sperm count (C, D), and serum E<sub>2</sub>(E, F) for exposed men and of same-age comparison groups [A, C, E; men who were 1–9 years of age in 1976 (22–31 years of age in 1998); B, D, F; men who were 10–17 years of age in 1976 (32–39 years of age in 1998). Median concentrations of TCDD quartiles (shown in parentheses) are expressed as parts per trillion on a serum lipid basis in 1976.

**Comment 17: The Reference Dose derived from Mocarelli et al. (2008) is flawed because the authors have not demonstrated that the control group was unexposed to dioxin. These 82 men were assumed to be unexposed.**

Specifically, Mocarelli et al. (2008) states: “Serum TCDD concentrations for the comparison groups were assumed to be ≤ 15 ppt in 1976 and < 6 ppt in 1998.” No measurements were made to verify this assumption.

**Comment 18: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because the results of the study have not been demonstrated to be biologically plausible.**

The results of this paper were that boys exposed to dioxin between the ages of 1 and 9 had decreases in sperm concentration when measured at the ages of 22-31, but young men exposed between the ages of 10-17 had *increases* in sperm concentration when measured at the ages of 32-39. Neither Mocarelli et al. (2008) nor EPA have explained the biological mechanism by which dioxin can have a negative effect on a 9 year old boy and a positive effect on a 10 year old boy.

**Comment 19: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because the results of the study are highly dependent on the arbitrary definition of two exposure groups by age.**

Mocarelli et al. (2008) state that 10-17 is the time period defined as puberty in boys. Hence, participants were grouped by ages 1-9 and 10-17. It is not clear that 10 is a reasonable assumption for the age of puberty in boys. Several sources were consulted including Medline Plus, National Institute of Health (2010), FamilyDoctor.org (2010), Kidshealth.org (2010), and Harvard University (Massachusetts General Hospital for Children) (2010), and those sources cite the age range of 12-16 as the average age of onset of puberty.

No data are presented on all exposed boys and men in a total group of 115 or groups defined with different cut-off ages. Because the first quartile of the 10-17 year old exposed boys had a 67% *increase* in sperm concentration compared to the 20% decrease in the 1-9 year old boys at about the same median dose (68 ppt versus 53 ppt), it is extremely important to understand the effects of placing 10 and 11 year old boys into the older category versus the younger category. It is very possible that the results of the entire analysis would evaporate if the two categories were defined as 1-10 and 11-17 or 1-11 and 12-17.

**Comment 20: The Reference Dose derived from Mocarelli et al. (2008) is based on the incorrect dose metric because it assumes that sperm concentration is causally influenced by 2,3,7,8-TCDD only and fails to consider the influence of other dioxin-like compounds.**

Mocarelli et al. (2008) postulate that TCDD exposure in young boys is decreasing sperm concentration in young men by a mechanism that involves the Ah receptor. Specifically, Mocarelli et al. (2008) states:

"TCDD and other dioxin-like chemicals produce their effects primarily through the aryl hydrocarbon receptor (AhR). Activation of AhR by dioxin, therefore, could be a mechanism by which androgen action is reduced; this could explain the observed decrease in sperm count in adults who were exposed to TCDD as young children (i.e., when Sertoli cell development is more testosterone dependent). This hypothesis is supported by the observation that *in utero* exposure of human males to maternal smoking causes reduced sperm counts in the offspring at adulthood; this probably is a result of reduced Sertoli cell number (Jensen et al. 2004; Storgaard et al. 2003) due to the action of polycyclic aromatic hydrocarbons present in cigarette smoke on AhR."

Mocarelli et al. (2008) also states:

"Because the only dioxin-like chemical involved with the Seveso incident was TCDD, we focused on TCDD for these analyses. If TCDD acts in concert with other dioxin-like chemicals in affecting sperm quality, the total dioxin toxic equivalency (TEQ) should be considered. In nine serum pools from females residing in the uncontaminated area in 1976, Eskenazi et al. (2004) found an average TEQ of 100 ppt."

If this is the case, then the dose of total 2,3,7,8-TCDD-Toxic Equivalents is relevant to the derivation of a RfD, not simply the dose of 2,3,7,8-TCDD. EPA's own policy requires risk assessors to assume that all dioxin-like compounds including other 2,3,7,8-substituted PCDDs and PCDFs as well as certain PCBs act on the Ah receptor and pose risks equivalent to TCDD when pro-rated with the use of the Toxic Equivalency Factors.

Most studies of people exposed to TCDD in Seveso, Italy focus solely on TCDD. However, it is clear that other dioxin-like congeners were released during the explosion, and people present at the time of the explosion were exposed to the complex mixture of dioxin-like compounds. For example, Baccarelli et al. (2008) studied women from 1994 to 2005 and measured their serum TCDD, PCDDs, PCDFs and co-planar PCBs. According to Baccarelli et al. (2008): "Maternal mean TCDD levels were 18.9 ppt (n = 51, range 1.4–309.5). Mean plasma TEQs were 44.8 ppt (n = 51, range 11.6–330.4) for PCDDs, PCDFs, and coplanar PCBs;..." Their Figure 2 provides plots of maternal plasma TCDD versus neonatal TSH in offspring and maternal PCDDs, PCDFs, and cPCBs versus neonatal TSH in offspring. The plots clearly show that most women's TCDD levels were 2.5 to 10 ppt, whereas the TEQ levels were 20 to 60 ppt. Thus, TCDD comprised only a small fraction of their total TEQ concentration, and neonates were exposed to far more TCDD-TEQ than they were to merely TCDD.

Similarly, the young boys exposed to dioxin and dioxin-like compounds in 1976 were exposed to far higher levels of TCDD-TEQ than they were to TCDD alone. Any RfD based on the TCDD dose alone is scientifically incorrect and *underestimates* the true RfD.

**Comment 21: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because the comparison group is ill defined.**

Mocarelli et al. (2008) states virtually nothing about the comparison group except: "we chose healthy blood donors from a nearby area..." Mocarelli et al. (2008) do not define how close the "nearby area" is to allow the reader to make a judgment as to whether the comparison men were exposed to TCDD-TEQ or not.

**Comment 22: The Reference Dose derived from Mocarelli et al. (2008) has inappropriately been divided by an Uncertainty Factor for intraspecies sensitivity despite the fact that EPA has defined pre-pubescent boys as a sensitive subpopulation.**

EPA (2010a) states: "males less than 10 years old can be designated as a sensitive population by comparison to older males who were not affected." Later, EPA applies a Human interindividual variability ( $UF_H$ ) of 3 stating the following: "A factor of 3 ( $10^{0.5}$ ) is used because the effects were elicited in sensitive populations. A further reduction to 1 was not made because the sample sizes were relatively small, which, combined with uncertainty in exposure estimation, may not fully capture the range of interindividual variability."

This  $UF_H$  is unnecessary because the men exposed as young boys not only are considered a sensitive population, but the alleged adverse effect of 20% reduction in sperm concentration in a single sample was only seen in this grouping of young boys. In older boys, the opposite effect was seen: an increase in sperm concentration. As noted elsewhere in these comments, this alleged "adverse" effect was not, in fact, adverse, because the 95<sup>th</sup> percentile range of the adjusted concentrations was well within the range of normal sperm concentrations for fertile men. The mean +/- the standard error for the entire group of 71 young men exposed as young boys was 43 to 55 million sperm/mL. The 95% confidence interval on the mean of the 18 young men in the first quartile was approximately 40 to 80 million sperm/mL. According to WHO (2010), the lower reference limit for sperm concentration is  $15 \times 10^6$  sperm/mL. Because of these factors, it is not necessary to apply a  $UF_H$  of 3 to the Point of Departure dose when deriving a RfD for TCDD or TCDD-TEQ.

**Comment 23: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because it is not based on an adverse effect. It is based on a 20% decrease in sperm concentration, but those decreased sperm concentrations are well within normal ranges for fertile men.**

As noted above, according to WHO (2010), the lower reference limit for sperm concentration is  $15 \times 10^6$  sperm/mL. Thus, a 20% decrease in the first quartile group resulted in a mean of about  $60 \times 10^6$  sperm/mL with a lower 95% confidence interval of  $40 \times 10^6$  sperm/mL (EPA 2010a) appears to agree that these sperm concentrations are not adverse. However, EPA (2010a) stated:

“Although a decrease in sperm concentration of 20% likely would not have clinical significance for an individual, EPA’s concern is that such decreases associated with TCDD exposures could lead to shifts in the distributions of these measures in the general population. Such shifts could result in decreased fertility in men at the low end of these population distributions. In the group exposed due to the Seveso accident, individuals one standard deviation below the mean are just above the cut-off used by clinicians (20 million/ml) to indicate follow-up for potential reproductive impact in affected individuals, indicating that a number of individuals in the exposed group likely had sperm concentrations less than 20 million/ml; EPA could not obtain the individual data to determine the exact number of men in this category.”

Thus, EPA is concerned that some men at the low end of the distribution will fall below a fertility level if they experience a 20% decrease in sperm concentration. However, there is no evidence presented by Mocarelli et al. (2008) or EPA that any young men in the TCDD exposed group fall below  $15 \times 10^6$  sperm/mL or even approach  $15 \times 10^6$  sperm/mL. Given a mean sperm concentration of  $48.6 \times 10^6$  sperm/mL and a standard error of  $5.5 \times 10^6$  sperm/mL, one would have to be 6 standard errors below the mean to reach the lower reference limit of  $15 \times 10^6$  sperm/mL.

**Comment 24: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because the effects noted show no dose-response relationship.**

As noted in Figure 2 from the paper, there is no difference between the sperm concentration or the sperm motility when the first, second, third and fourth quartile groups are compared. If dioxin exposure was the cause of any effects seen in semen quality of the experimental group of young men who were exposed from ages 1-9, there would have been a greater effect seen as the quartile doses increased from 68 ppt to 142 ppt, 345 ppt and 733 ppt. In fact, as seen in the young men exposed at ages

10-17, the quartiles show no trends whatsoever, with effects going up-down-up-down compared to the comparison group. With no dose-responsiveness, there is little basis for concluding that the effects seen in the young men exposed as 1-9 year-old boys is causally associated with dioxin.

**Comment 25: The Reference Dose derived from Mocarelli et al. (2008) is scientifically flawed because EPA used the incorrect dose for the LOAEL.**

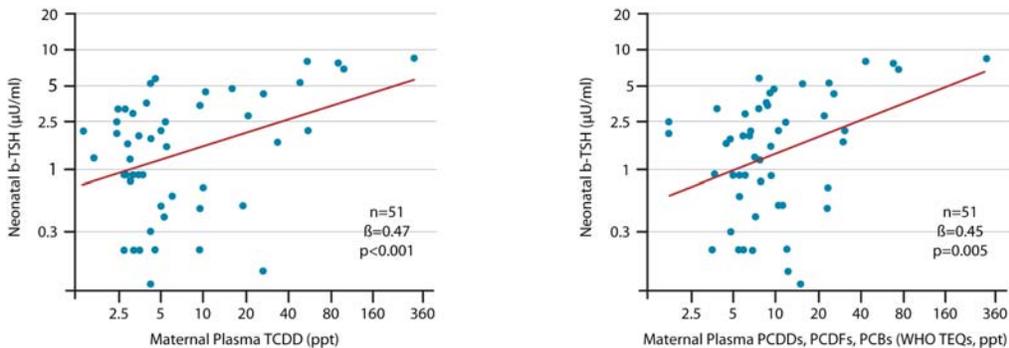
EPA (2010a) used 68 ppt as a LOAEL, but the authors did not state that this value was statistically significantly different from the comparison group. They did, however, state that 113 ppt "adversely affected sperm concentration and total motile sperm count." Accordingly, EPA has used an incorrect dose as the Point of Departure for the RfD. In fact, the only data shown in this paper that was demonstrated to be statistically significantly different from the comparison group for the young men exposed as 1-9 year-olds is the mean of the entire group, 210 ppt. This dose of 210 ppt would have been a Point of Departure if EPA had chosen to only consider dose levels that were shown to be statistically significantly different from controls.

**COMMENTS ON BACCARELLI ET AL. (2008)**

**Comment 26: The Reference Dose derived from Baccarelli et al. (2008) is based on the incorrect dose metric because it assumes that neonatal TSH levels are causally influenced by 2,3,7,8-TCDD only and fails to consider the influence of other dioxin-like compounds.**

Baccarelli et al. (2008) studied women from 1994 to 2005 and measured their serum TCDD, PCDDs, PCDFs and co-planar PCBs. According to Baccarelli et al. (2008): "Maternal mean TCDD levels were 18.9 ppt (n = 51, range 1.4–309.5). Mean plasma TEQs were 44.8 ppt (n = 51, range 11.6–330.4) for PCDDs, PCDFs, and coplanar PCBs;..." Their Figure 2 provides plots of maternal plasma TCDD versus neonatal TSH in offspring and maternal PCDDs, PCDFs, and cPCBs versus neonatal TSH in offspring. The plots clearly show that most women's TCDD levels were 2.5 to 10 ppt, whereas the TEQ levels were 20 to 60 ppt. Thus, TCDD comprised only a small fraction of their total TEQ concentration, and neonates were exposed to far more TCDD-TEQ than they were to merely TCDD.

FIGURE 12  
FIGURE 2 FROM BACCARELLI ET AL. (2008)



EPA should have focused their attention on the TCDD-TEQ data which was presented clearly in the paper. Instead of relying on the predicted maternal TCDD concentration of the >5 µU/mL group as the Point of Departure (270 ppt), EPA should have relied on the maternal TCDD-TEQ concentration of the >5 µU/mL group, which would exceed 270 ppt. The resulting RfD would have been higher had EPA focused on all dioxin-like compounds that could have affected the thyroid hormone levels in the exposed population assuming that the WHO TEFs are appropriate for this response. As stated in the following comment, 5 µU/mL is not an adverse effect, so EPA should also have relied on a higher TSH concentration to define an adverse effect level.

**Comment 27: The RfD derived from Baccarelli et al. (2008) is scientifically flawed because it is not based on an adverse effect. It is based on a thyroid stimulating hormone (TSH) level of 5 µU/mL in neonates, which is a normal TSH level for 72-hour-old neonates, unassociated with any adverse effects.**

The TSH benchmark applied to neonates in the Baccarelli study, 5 µU/mL, is a criterion that was established for identifying possible iodine deficiency in a population. As stated in the WHO/UNICEF/ICCIDD Consultation (1993) on assessing iodine deficiency:

“a TSH cut-off of 20-25 mU/L [µU/mL] whole blood (approximately 40-50 mU/L serum) is commonly used to screen for congenital hypothyroidism. IDD [iodine deficiency disorder] may be present with TSH levels which are only mildly elevated. [...] a cut-off of 5 mU/L whole blood may be appropriate for epidemiologic studies of IDD.”

The benchmark for identifying clinical hypothyroidism in neonates is typically 20 µU/mL or higher. Guidance from the American Academy of Pediatrics for congenital

hypothyroidism screening recommends a TSH criterion of 20-25 mU/L [ $\mu\text{U}/\text{mL}$ ] for samples taken at least 48-96 hours post partum (Rose and Brown 2006).

The highest TSH level reported in the Baccarelli data set used for the RfD was less than 10  $\mu\text{U}/\text{mL}$ . Based on these TSH levels and the typical reference ranges used for assessing clinical hypothyroidism, none of the infants from the Baccarelli study would have been identified as having hypothyroidism. Further, these levels would not likely have prompted a clinical follow-up, unless accompanied by signs of a dysmorphic thyroid gland and a confirmation of the elevated TSH values with a second blood test.

The 5  $\mu\text{U}/\text{mL}$  benchmark established by WHO/UNICEF/ICCIDD (1993) is not a threshold above which adverse effects are expected. Rather, it is a level that has been used to mark the point at which TSH levels will begin to predict iodine deficiency.

The Baccarelli authors state that the recall threshold for further investigation in the Lombardy Region is set at a blood TSH level  $>10 \mu\text{U}/\text{mL}$  when samples are taken 72 hours post partum. Despite being a relatively low benchmark as compared with the ranges cited by the WHO/UNICEF/ICCIDD (1993) consultation, it is still notable that in applying this benchmark, the authors are implicitly acknowledging that the 5  $\mu\text{U}/\text{mL}$  benchmark is of no clinical relevance.

In the regression analysis plots from Baccarelli (Fig. 2), which are cited by EPA as the basis of the RfD derivation (See Reanalysis, Appendix D), if a benchmark of 10  $\mu\text{U}/\text{mL}$  had been used, rather than 5  $\mu\text{U}/\text{mL}$ , the corresponding POD (in terms of a maternal plasma TCDD concentration) would be approximately  $>1200$  ppt, as compared with 270 ppt. The resulting RfD would be about 5-fold higher. Of course, if a 10  $\mu\text{U}/\text{mL}$  benchmark was applied to the Baccarelli regression analysis, there would be little, if any, basis for comparing exposures, since there were, according to Figure 2, no data points exceeding 10  $\mu\text{U}/\text{mL}$ .

Therefore, the fact that a few neonatal blood samples from the Baccarelli study exceeded 5  $\mu\text{U}/\text{mL}$  posed, by itself, of no clinical significance. Comparing individual data points against the  $>5 \mu\text{U}/\text{mL}$  benchmark is really not meaningful, but even in doing so, the maximum TSH level observed by Baccarelli would only be indicative of a risk of mild iodine deficiency, and iodine deficiency is not caused by exposure to dioxin or any other chemical. It is caused by ingesting too little iodine in the diet.

As stated above, there is really no basis in the Baccarelli study for concluding that dioxin in their study could be a cause of CH, since CH is almost always accompanied by newborn TSH levels of  $>40 \mu\text{U}/\text{mL}$  and much higher. Thus, EPA is distorting the implications of the Baccarelli findings. The profound neurodevelopmental outcomes

that EPA mentions in reference to TSH levels have been the result of profound hypothyroidism, in many cases due to severe iodine deficiency, not from any of the modest changes in TSH levels as observed by Baccarelli.

In summary, neonatal TSH levels in the range of 5 – 20 µU/mL are not diagnostic of hypothyroidism, and at most would only signal the need for a second test or an assessment of other thyroid risk factors. Such levels, particularly those <10 µU/mL are not by themselves considered a problem by the American Academy of Pediatrics and the National Academy of Clinical Biochemistry and would not prompt treatment (Demers and Spencer 2002 ; Rose and Brown 2006).

Furthermore, neonatal TSH levels in excess of 5 or even 10 µU/mL are quite common. According to Lott et al. (2004), 22.5% of 6,852 newborns tested at 72-95 hours after birth had TSH levels of 6 µU/mL or higher. The full data set is presented below.

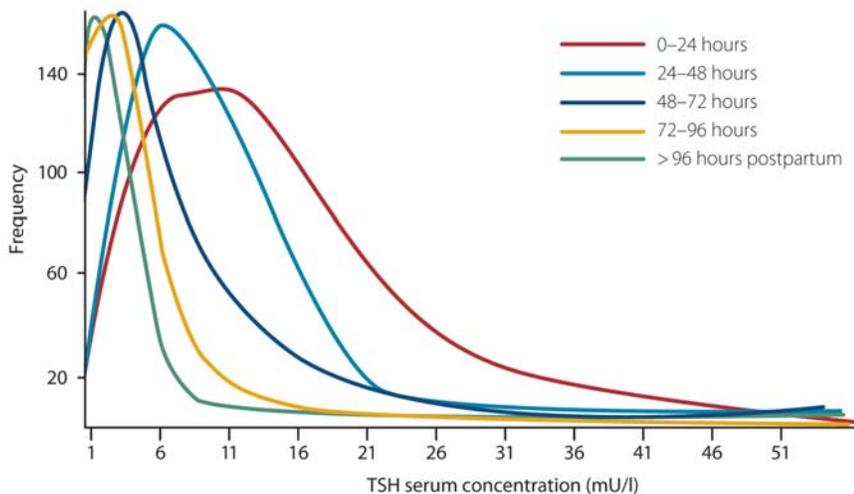
**TABLE 9  
FRACTION OF NEONATES ABOVE 6 µU/mL FROM LOTT ET AL. (2004)**

Age Tested (Hours After Birth)	Number Tested	Fraction Above 6 µU/mL
<24	2,642	80.5%
24-47	100,696	75%
48-71	39,643	37%
72-95	6,852	22.5%
>= 96	11,411	12%

The data of Lott et al. (2004) are presented graphically below.

**FIGURE 13  
NEONATAL TSH CONCENTRATIONS BY TIME OF TESTING, FIGURE 3 FROM LOTT ET AL., (2004)**

Figure 3. The shift in serum thyrotrophin (TSH) 5% frequency distribution at various time intervals postpartum (adapted from Lott et al.<sup>16</sup>).



**Comment 28: The findings of the Baccarelli study should be classified as “hypothesis-generating” and not used as the basis for drafting public health criteria. The correlations observed, for several reasons are likely to be spurious associations and not indicative of a dose-related response to dioxin exposure.**

The Baccarelli study is plagued by too many confounding variables to be considered for use in defining the dose-response relationship for TCDD (or TCDD-TEQ) human exposures. Chief among these is the iodine status of the study population. The authors state that data on maternal iodine intake were not available. The authors address this point, stating that “there is no indication that exposed and unexposed women had differences in iodine intake in the study period”. The authors also mention the geographic proximity and the comparability of the exposed and reference populations.

This is inadequate treatment for a variable that has a direct and measurable effect on basal TSH levels. TSH levels are highly sensitive to changes in iodine status in a population or an individual. As noted above, the TSH benchmarks used by Baccarelli are in fact benchmarks intended for the assessment of iodine deficiency on a global scale.

While in the U.S., the general population is generally considered iodine replete, many countries in Middle-East, Asia, and Europe, including Italy, are not. In fact, according

to a Global Scorecard on prevention of iodine deficiency (ICCIDD, 2010), 55.7% of the Italian population has low urinary iodine excretion (UIE) and Italy has a goiter rate of 13.9%.

The implications are significant. If the Seveso population has low iodine intakes, with a proportion of residents having a deficiency, which reflects the national average, this could have had a noticeable effect on the neonatal TSH data. It would bring the findings into question and invalidate any conclusions based on the number of samples that were above a 5 or 10  $\mu\text{U/mL}$  benchmark, as these values are very common (20-40%) in populations with moderate iodine deficiency. Therefore, the authors explanation that potential iodine-related effects would affect all study groups evenly, and therefore, would not impact the findings, is questionable.

Another potentially significant confounder in the Baccarelli study is the co-exposure to other persistent organic chemicals, particularly polychlorinated biphenyls and diphenyl ethers. In a separate comment, it is noted that other dioxin-like compounds (PCDDs and PCDFs other than TCDD, and dioxin-like PCBs) should be included in the dioxin dose (as TCDD-TEQ) that is used in the dose-response assessment. However, the continuing presence of these compounds plus non-dioxin-like PCBs, and polychlorinated and polybrominated diphenyl ethers (PC/PBDEs) in the normal diet of Seveso residents is also something that presents a special problem for the Baccarelli study. This is because PCBs and, perhaps to a lesser extent the PC/PBDEs, exhibit thyroid hormone disruption through various mechanisms of action, which might not be shared by TCDD. In fact, there is much greater accumulation of evidence implicating PCBs in thyroid hormone modulation than there is for TCDD. Further, supporting the hypothesized effects of PCBs are animal correlates, which is not the case for TCDD. Background exposures incurred by the Seveso residents show that, even as a TCDD-TEQ, the PCB levels measured in Seveso residents near the time of the Baccarelli study were about 6 ppt (lipid adjusted) (Landi et al. 1998) The levels of total PCB levels were much higher (Landi, et al., 1998; Eskenazi et al. 2004, Warner, et al. 2005). An abundance of research has shown that the non-dioxin-like PCBs are among the most active compounds with respect to thyroid hormone disruption. This class of PCBs is in general found at ambient levels that are much higher than concentrations of TCDD and that are active in thyroid hormone disruption.

Many more studies regarding a possible relationship between PCBs and thyroid hormone effects have been published, as compared to those examining possible TCDD-related effects. The findings from the PCB studies have been mixed overall. Further, looking at the studies that examine neonatal TSH levels specifically (Ribas-Fito et al., 2003; Koopman-Esseboom et al., 1994), on PCBs are mixed, but interestingly, correlations between dose and response are usually poor, or nonexistent

when measuring the PCB dose in terms of a TCDD-TEQ (Ribas-Fitó et al. 2003; Chevier et al. 2007). Chevier et al. (2007) conducted regression analyses examining 3 different PCB subclasses, based on their enzymatic or biochemical-based activities which might lead to effects on thyroid hormones. They only found significant effects when looking at the non-dioxin-like PCBs and these associations could be strong: For the most active PCB subclass, each 10-fold increase in the sum of these PCBs was associated with a 29% increase in (neonatal) TSH. However, the TCDD-TEQ of dioxin-like PCBs were not significantly associated with neonatal TSH levels.

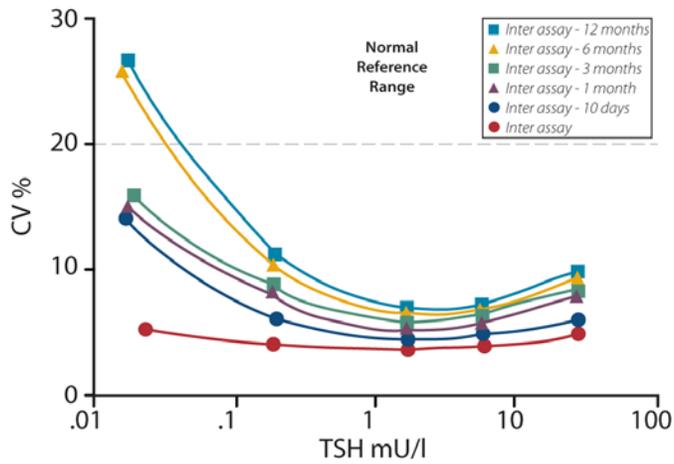
**Comment 29: Given the sensitivity of TSH to confounding influences and experimental error, the Baccarelli study should have included some confirmatory analyses before concluding that the observed changes in TSH were real.**

TSH levels in neonates could be expected to be influenced by the following: time of day, sleep pattern, type of birth, birth weight, nutritional factors, and drugs (passed on through the mother) and non-thyroidal illness. These have the potential to act as confounding variables. While not expected to have an association with TCDD exposures in the study groups, it is troublesome when the regression based on TSH could be heavily influenced by one or two data points. There are methodological influences affecting TSH data as well, including the time since birth, collection of blood, and handling and storage of blood samples.

Given the uncertainty in TSH measurements, the Baccarelli study authors should have measured T4 (thyroxine) as well as TSH and should have taken a confirmatory blood sample for TSH analysis. As noted by the study authors, elevated levels of TSH are usually the result of low levels of T4. For this reason, the measurement of T4 in conjunction with TSH is standard operating procedure for most newborn screening programs (with some programs measuring T4 secondary to an abnormal TSH level, and others measuring TSH secondary to T4). Taking a second, confirmatory sample is also standard, recommended procedure for diagnosing hypothyroidism in newborns (Rose and Brown 2006).

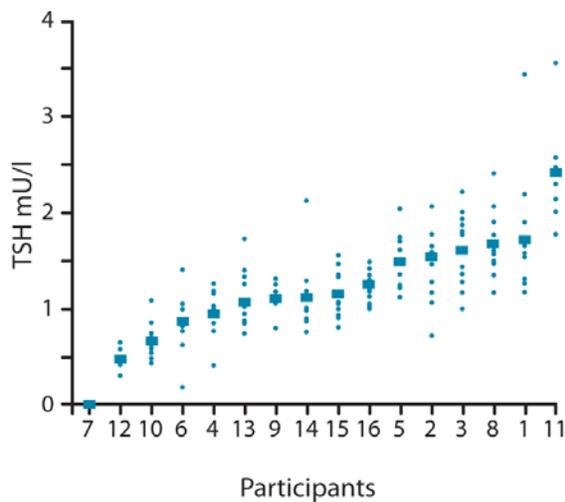
It is particularly important to obtain repeat measurements for TSH because TSH levels are highly variable in the population. The following figures from Spencer et al. (1996) and Andersen et al. (2002) demonstrate that TSH levels vary widely even within the same individual over a short period of time.

**FIGURE 14**  
**VARIABILITY IN TSH MEASUREMENTS FROM SPENCER ET AL. (1996)**



Erosion of TSH inter assay precision profiles (10 or more analysis of human serum pools) across time.

**FIGURE 15**  
**VARIABILITY IN TSH MEASUREMENTS FROM ANDERSEN ET AL. (2002)**



**Comment 30: The Reference Dose derived from Baccarelli et al. (2008) does not reflect the “best available science” because it uses the outdated Lowest Observed Adverse Effect Level approach rather than the Benchmark Dose approach which defines current EPA policy.**

As noted above, EPA currently derives Reference Doses (RfDs) by the use of the Benchmark Dose approach wherein its Benchmark Dose Software (BMDS) is employed to derive a benchmark dose – low (BMDL) for the adverse effect of interest (EPA 2000a). This approach is superior to the simplistic use of Lowest Observed Adverse Effect Levels to define the Point of Departure for RfD derivation.

In this case, EPA has available figures in the paper that provide all of the raw data, so benchmark dose modeling could have been performed to define an appropriate BMDL as the Point of Departure. In this manner, the entire dataset is used to define a dose at which a prescribed fraction of the population exhibits the designated effect.

**SCIENCE POLICY COMMENTS****Comment 31: The proposed OSF and RfD are flawed because they do not adhere to the EPA's own Risk Characterization Policy of transparency, clarity, consistency and reasonableness (TCCR).**

EPA's Risk Characterization Policy (EPA 2000b) calls for a transparent process and products that are clear, consistent and reasonable. All risk assessments have a risk characterization product, but effective characterization depends on TCCR. According to EPA, TCCR is the key to a successful risk characterization.

EPA (2000b) defines transparency, clarity, consistency and reasonableness as the keys to any successful risk assessment. If a process is transparent, then "it ensures that any reader understands all the steps, logic, key assumptions, limitations, and decisions in the risk assessment, and comprehends the supporting rationale that lead to the outcome." By making a document transparent, EPA (2000b) finds that the information will be reported in a manner that will be understandable to the audience and that they will be able to follow all of the arguments presented. Documents should also be consistent with all applicable policies, guidance, and scientific methods, although not at the expense of innovation. EPA defines the reasonableness criterion as the one that presents the findings using the best available scientific information (EPA 2000b). The approach used in the risk assessment should be based on a logical approach following relevant guidance.

Lack of Transparency

The development of the proposed OSF and RfD is not transparent because it does not rely on the large quantity of toxicological assessment work that has been undertaken since the 2003 Reassessment document. In addition, EPA (2010a) does not explain why they did not pursue benchmark dose modeling for the two human datasets used to derive the RfD. No explanations were given. EPA states merely that "modeling of a benchmark dose lower confidence bound [BMDL] was not possible given the data presented in these studies."

Lack of Clarity

The proposed OSF and RfD lack clarity, because EPA has not stated the need for the action at this time. As noted elsewhere in these comments, dioxin emissions to the environment have been steadily decreasing, as have dioxin levels in foodstuffs and human tissues. EPA has not made any clear statement that there is any imminent

threat, and clearly cannot do so based on the facts and *best available science*, so the proposed action contradicts its own risk characterization policy.

#### Lack of Consistency

The proposed OSF and RfD lack consistency. The OSF is not consistent with the EPA's most recent carcinogen risk assessment guidance. The OSF is also not consistent with international regulation of dioxin, which has been done elsewhere around the world using a threshold approach reflecting the known mode of action as a threshold carcinogenic agent. Also importantly, the OSF is not consistent with EPA's Toxic Equivalency Approach which states that all dioxin-like compounds act in a similar manner as does TCDD. The EPA in this document has ignored the impacts of all other dioxin-like compounds in performing its dose-response assessment. The RfD lacks consistency with other RfDs that EPA has derived in recent years, because it was not derived by the use of benchmark dose modeling as is the current EPA policy.

#### Lack of Reasonableness

The proposed OSF and RfD are not reasonable. Both are not reasonable because dioxin releases, exposures and body burdens are decreasing in the population and have been for over 20 years. There is no public health imperative to increase the stringency of regulation of a problem that is vanishing in its public health significance.

Specifically, the OSF is not reasonable because it is based on a low dose linear extrapolation method that does not match its known mode of action. It is also based on marginally statistically significant results for two cancer sites that are not associated with dioxin exposure in other epidemiological studies. It is also based on the dose of TCDD when it is clear that the workers who were exposed to TCDD in their workplace were also exposed to other dioxin-like compounds that would raise the OSF if quantitatively taken into account. It is unreasonable because the implications of such a high OSF is that a significant proportion of the population would be experiencing cancer effects due to exposures to TCDD-TEQ when there is no evidence to support such a conclusion.

The RfD is not reasonable because it is based on two endpoints that are not *adverse* effects. Also, it is unreasonable because the implications of such a low RfD is that a significant proportion of the population would be experiencing effects on their thyroid function and semen quality due to exposures to TCDD-TEQ when there is no evidence to support such a conclusion.

**Comment 32: The derivation of the proposed OSF and RfD is flawed because it does not adhere to the Information Quality Act (IQA) and Agency Guidelines for Implementing the Act.**

The IQA, Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658) requires the Office of Management and Budget (OMB) to issue federal agency-wide guidelines that “provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies” (Federal Register, Vol. 67, No. 38, February 22, 2002). OMB issued guidelines directing federal agencies to:

1. “Issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency, ...
2. Establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines..., and
3. Report to the Director the nature and number of complaints regarding the accuracy of the information disseminated by the agency and how the complaints are handled.”

In response, the EPA developed *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (EPA 2002a). In addition to establishing policies and procedures, the Guidelines provide performance goals for the Agency as follows:

- “Disseminated information should adhere to a basic standard of quality, including objectivity, utility, and integrity.
- The principles of information quality should be integrated into each step of EPA’s development of information including creation, collection, maintenance, and dissemination.
- Administrative mechanisms should be flexible, appropriate to the nature and timeliness of the disseminated information, and incorporated into EPA’s information resources management and administrative practices.”

To comply with the OMB guidelines, EPA (2002a) adapted the quality principles of the Safe Drinking Water Act (SDWA) Amendments of 1996 in preparing its guidelines. In those guidelines, EPA states:

“The substance of the information is accurate, reliable and unbiased. This involves the use of:

- (i) The best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and
  - (ii) Data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justify the use of the data).
- (A) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable. In a document made available to the public, EPA specifies:
- (i) Each population addressed by an estimate of applicable human health risk or each risk assessment endpoint, including populations if applicable, addressed by any estimate of applicable ecological risk;
  - (ii) The expected risk or central estimate of human health risk for the specific populations affected or the ecological assessment endpoints, including populations if applicable;
  - (iii) Each appropriate upper-bound or lower-bound estimate of risk;
  - (iv) Each significant uncertainty identified in the process of the assessment of risk and studies that would assist in resolving the uncertainty; and
  - (v) Peer-reviewed studies known to the Administrator that support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.”

The intent in developing these guidelines is to direct the Agency to use the “best available” information at the time the assessment is made. EPA qualified their position by indicating that because scientific knowledge is continually expanding and changing,

information included in documents could need to be updated based on new information.

The applicability of these guidelines in the context of the proposed OSF and RfD is that EPA has policy directing it to utilize the best available and most current information when developing information to be disseminated to the public. EPA also indicated that the Agency is sometimes required to make determinations based on limited amounts of information. This is not the case for the proposed toxicological criteria for dioxin. Rather, for dioxin, there is a wealth of information available in the literature. It is incumbent upon the Agency to incorporate the currently available information into the development of the toxicity values proposed in May 2010.

EPA does provide guidance for emergency or "other time critical circumstances." Releasing the proposed OSF and RfD in May 2010 did not correspond to a time critical circumstance nor did an emergency situation exist requiring the Agency to act. Instead, by moving forward with the release of the proposed OSF and RfD, EPA acted contrary to its own guidelines which indicated that "In the Agency's development of 'influential' scientific risk assessments, we intend to use all relevant information, including peer reviewed studies, studies that have not been peer reviewed, and incidental information; evaluate that information based on sound scientific practices as described in our risk assessment guidelines and policies; and reach a position based on careful consideration of all such information" (EPA 2002a, page 26).

To the extent a formal request pursuant to EPA's IQA procedures set out in EPA 2002a is necessary, the sponsors of these Comments specifically request EPA to reconsider the inaccurate information it has disseminated in its Response to the NAS' Comments, and in doing so consider and respond to these Comments as well as the numerous other comments being submitted by the regulated community, academia and other members of the public. This request for reconsideration is incorporated by reference in each of the specific comments herein that reference the IQA and the EPA's IQA policy and procedures set out in EPA 2002a.

**Comment 33: EPA did not follow its own policy by not preparing a cost benefit analysis of the consequences of implementing the proposed OSF and RfD.**

According to EPA (2006b), EPA should identify all of the impacts on stakeholders (e.g., federal, state, or local governments). In addition to the monetary benefits or costs of the policy, EPA should also discuss the non-monetary impacts, positive and negative, of the implementation of these toxicological criteria, which will affect environmental regulations of all media, including soil, drinking water, surface water, food, air and consumer products.

**Comment 34: The document proposing an OSF and a RfD does not adhere to the IQA and EPA's Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the EPA (2002a), because it fails to present any information that demonstrates that dioxin in any environmental media presents a *de minimis* risk to human health.**

The IQA requires Federal agencies to ensure and maximize "the quality, objectivity, utility, and integrity of information" that they disseminate. EPA has issued its own guidelines for adhering to the IQA, and in those guidelines, EPA (2002a) states that documents presented to the public must present studies that "fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data." EPA (2002a) also requires documents released to the public to present information on population risks.

As noted elsewhere in these comments, several recent reports have been published that demonstrate that dioxin in soil is a *de minimis* exposure pathway and does not contribute substantially to population risk from dioxin and furan congeners. Studies such as Garabrant et al. (2009), ATSDR (2005) and Dilberto et al. (2008) should have been thoroughly discussed in any document about dioxin's risks to human health, including *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*.

**Comment 35: EPA did not adhere to Executive Order 12866 in the Draft Interim PRG document.**

The key points required under Executive Order 12866 are that federal agencies need to:

- Promulgate only those regulations that are needed to protect the health of the public. In doing this, an agency should consider both the costs and benefits of implementing a regulation or policy.
- Evaluate the costs and benefits of the regulations.
- "Base decisions on the best, reasonably obtainable scientific, technical, economic, and other information concerning the need for, and consequences of, the intended regulation" (Federal Register 1993).
- "Tailor its regulations to impose the least burden on society, including individuals and businesses of differing sizes" (Federal Register 1993).

The following lists just a few of the reasons that EPA (2010a) does not comply with Executive Order 12866.

1. EPA did not demonstrate the need to derive a new OSF and a RfD for dioxin.
2. EPA did not provide a cost-benefit analysis of implementation of this policy. The Agency did not demonstrate that the overall benefit to public health by requiring these toxicological criteria be used to assess and remediate sites and regulate emissions to the environment.
3. EPA did not base its proposed OSF and RfD on the best reasonably obtainable scientific and technical information. Many recent scientific studies have demonstrated that risk to humans from dioxin is low and decreasing. The only justification for increasing the OSF and deriving a RfD would be the presence of some imminent threat to human health from dioxin exposures. EPA has not made any clear statement that any such imminent threat exists.
4. When proposing the Interim PRGs in November 2009, EPA indicated that "Regions performing five-year-reviews of CERCLA remedial sites where soils contaminated with dioxin or other dioxin-like compounds have been left in place should consider this guidance on recommended interim PRGs when evaluating whether original remedies in the Records of Decision (RODs) remain protective for the contaminated areas." Clearly, the issuance of a higher OSF and a new RfD will affect all future five-year reviews of CERCLA sites. EPA did not provide information on the number of sites potentially affected by these new toxicological criteria nor did it provide an estimate of the costs likely to be incurred at these sites by both the Government under Fund-Lead or State-Lead sites or responsible parties. The changes in toxicological criteria also impact RCRA sites and the costs associated with implementation for these sites also were not considered in the development of these toxicological criteria and the issuance of this document.

**Comment 36: The Draft Interim PRG document does not adhere to the IQA and EPA's Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the EPA (2002a), because it fails to quantify the impacts of the proposed OSF and RfD on population risks.**

The IQA requires Federal agencies to ensure and maximize "the quality, objectivity, utility, and integrity of information" that they disseminate. EPA has issued its own guidelines for adhering to the IQA, and in those guidelines, EPA (2002a) states that

documents presented to the public must present information on “the expected risk or central estimate of human health risk for the specific populations affected ...”

If EPA had explicitly assessed the impacts of the proposed action on the risks to the general population, as their own policy dictates, they would have found that there will be no meaningful risk reduction to the general population, or even sensitive subpopulations, resulting from the issuance of a new OSF and a RfD.

In addition, EPA has failed to evaluate the potential that the proposed OSF and RfD may cause a redistribution of human health risks among the population, possibly shifting *hypothetical* risks from dioxins in soils assuming incidental soil ingestion to *actual* risks from dioxins and other constituents to other populations, due to releases that will occur during site remediation activities.

**Comment 37: EPA's proposed OSF and RfD were not developed in accordance with EPA's Science Plan for Activities Related to Dioxins in the Environment because they do not provide an “analysis of relevant new key studies.”**

EPA has not followed the stated “plan” because the proposed OSF and RfD have not considered many of the recent publications that address dioxin toxicology. A very short list of important papers that EPA has not considered includes:

Budinsky, R.A., J.C. Rowlands, S. Casteel et al. 2008. A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. *Chemosphere* 70:1774–86.

Budinsky, R.A., C.R. Kirman, L.J. Yost, B.F. Baker, L.L. Aylward, J.M. Zabik, J.C. Rowlands, T.F. Long and T. Simon. 2009. Derivation of Soil Cleanup Levels for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Toxic Equivalence (TEQ<sub>D/F</sub>) in Soil Through Deterministic and Probabilistic Risk Assessment of Exposure and Toxicity. Presentation at Society of Toxicology Annual Meeting. March.

Charnley, G. and R.D. Kimbrough. 2006. Overview of exposure, toxicity and risks to children from current levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds in the USA. 2005. *Food and chemical Toxicology* 44:601-615.

Garabrant, D.H., A. Franzblau, J. Lepkowski, B.W. Gillespie, P. Adriaens, A. Demond, E. Hedgeman, K. Knutson, L. Zwica, K. Olson, T. Towey, Q. Chen, B. Hong, C-W. Chang, S-Y. Lee, B. Ward, K. LaDronka, W. Luksemburg and M. Maier. 2009. The University of Michigan Dioxin Exposure Study: Predictors of human serum dioxin concentrations in Midland and Saginaw, Michigan.

Hays, S.M. and L.L. Aylward. 2003. Dioxin risks in perspective: past, present, and future. *Regulatory Toxicology and Pharmacology* 37:202-217.

Kimbrough R.D., C.A. Krouskas, M. Leigh Carson, T.F. Long, C. Bevan, and R.G. Tardiff. 2009. Human uptake of persistent chemicals from contaminated soil: PCDD/Fs and PCBs. *Regul Toxicol Pharmacol.* 2009 Dec 24; [Epub ahead of print], Center for Health Risk Evaluation P.O. Box 15452 Washington, DC 20003, United States.

LaKind, J.S., S.M. Hays, L.L. Aylward and D.Q. Naiman. 2009. Perspective on serum dioxin levels in the United States: an evaluation of the NHANES data. *Journal of Exposure Science and Environmental Epidemiology* 19:435-441.

**Comment 38: EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments did not perform any evaluation of the implications of the proposed actions to determine if the actions will actually produce a net reduction in risk to human health.**

One of the key requirements of Executive Order 12866 is that regulatory agencies should consider both the costs and benefits of implementing a regulation or policy. Even if EPA's *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* were deemed to be exempt from Executive Order 12866, EPA should still have performed a detailed assessment of the impacts of the proposed actions, and they should have described why it was exempt.

Risk assessment specialists are often asked to prepare "comparative risk assessments" to determine how the risks associated with mitigating or remediating a problem compare to the risks posed by the original problem. In other words, regulatory agencies need to ensure that the proposed "solution" does not pose more risk than the "problem" before approving a proposed mitigation or remediation plan.

More broadly, the National Environmental Policy Act of 1969 (42 USC 4321) also requires that the consequences of planned actions be carefully assessed before the actions are taken. NEPA requires that the Federal government "attain the widest range of beneficial uses of the environment without degradation, risk to health or safety, or other undesirable and unintended consequences." Procedurally, NEPA requires that the Federal government shall:

"Include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on –

- (i) the environmental impact of the proposed action,
- (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,
- (iii) alternatives to the proposed action..”

Federal laws and regulations governing the remediation of hazardous waste *require* that the risks posed by proposed remedial actions be carefully considered before decisions are made. CERCLA (Superfund) regulations (40 CFR 300.430) state:

“The short-term impacts of alternatives shall be assessed considering the following: (1) short-term risks that might be posed to the community during implementation of an alternative; (2) potential impacts on workers during remedial action and the effectiveness and reliability of protective measures; (3) potential environmental impacts of the remedial action and the effectiveness and reliability of mitigative measures during implementation.”

EPA elaborates on interpretation of these regulations in its guidance for conducting remedial investigations and feasibility studies under CERCLA (EPA 1988) by requiring that alternatives remedies be evaluated with respect to their respective effects on human health and the environment.

EPA guidance says that the following factors should be addressed as appropriate for each alternative:

- “Protection of the community during remedial actions – this aspect of short-term effectiveness addresses any risk that results from implementation of the proposed remedial action, such as dust from excavation, transportation of hazardous materials, or air-quality impacts from a stripping tower operation that may affect human health.
- Protection of workers during remedial actions – this factor assesses threats that may be posed to workers and the effectiveness and reliability of protective measures that would be taken.
- Environmental impacts – this factor addresses the potential adverse environmental impacts that may result from the construction and implementation of an alternative and evaluates the reliability of the available mitigation measures in preventing or reducing the potential impacts.

...Alternatives should consider the potential threat to human health and the environment associated with excavation, transportation, and redisposal, or containment....Offsite transport and disposal without treatment is the least favored alternative where practicable treatment technologies are available.”

This required standard practice when assessing remedial options on specific sites should also be followed here when EPA proposes to issue an increased OSF and a new RfD that are applicable broadly to all sites and environmental regulations. In fact, it is more important for EPA to follow its site-specific guidance when issuing a generic policy with broad implications than it is when an individual site is being assessed. EPA has proposed a massive program without considering the costs to health and safety associated with its implementation. The many risks posed by the EPA's proposed new toxicological criteria that must be evaluated include:

- Increased risks posed by dioxin and furan transfers
- Increased fatality rates due to automobile and truck traffic
- Increased injury rates due to automobile and truck traffic
- Increased cancer and respiratory injury rates due to increased vehicle emissions
- Increased effects on global climate change due to increased vehicle emissions
- Increased traffic due to delivery of construction materials and disposal of waste
- Increased injury and fatality rates from remedial construction activities

With a targeted program, such risks might be *de minimis*, but the EPA is proposing a program that will necessarily employ hundreds or thousands of workers at hundreds of locations. Risks created by such a large program can be significant and must be weighed against the benefits that the program is intended to accomplish. Each of these risks to public health is discussed briefly below to outline the assessment that must be done by EPA to ensure that the actual risks of the proposed action do not outweigh the hypothetical risks that are being addressed by the program.

#### Dioxin and Furan Transfers

Automobiles, trucks and earth moving equipment are fueled either by gasoline or diesel fuel. Vehicles and construction equipment emit dioxins and furans, so EPA should be required to assess the emissions of dioxins and furans into the atmosphere to determine if the remedial actions caused to be undertaken by the changes in the dioxin toxicological criteria actually cause a net decrease in

exposures of the general population to dioxins and furans, or whether the remediation of dioxins and furans is replaced by new dioxins and furans from vehicle and equipment exhaust. In addition, when dioxin-containing soils or sediments are disturbed by land moving equipment either for consolidation and capping purposes or for transfer to trucks for off-site disposal, dioxins and furans will be released to the air and affect nearby adjacent receptors. Transportation to off-site locations can cause emission of dioxin-containing dust and vapor during the trip to the off-site treatment or disposal site, affecting people far from the site of the initial soil removal. Transfer operations at the off-site treatment or disposal site also cause releases of dioxin-containing dust and vapor. Lastly, treatment of dioxin-containing media in a combustor or a gasifier facility will have its own dioxin and furan emissions from the facility stack.

EPA must be held accountable for assessing these comparative risks to ensure that there is a net risk reduction that will occur as a result of any actions that are taken based on the proposed toxicological criteria. In addition to assessing the dioxin risks to the population as a whole, EPA must ensure that dioxin associated risks to human health are not transferred from one subpopulation to another. EPA must address these issues in a quantitative fashion before issuing such an important policy as the Interim PRGs.

#### Traffic Accidents and Fatalities

The implementation of site remediation required by the proposed toxicological criteria will involve hundreds or thousands of workers in many different states working for many years. EPA should make assumptions about the number of million vehicle miles traveled over the period of the program. After consulting National Highway Traffic Safety Administration statistics, such as NHTSA 2005, EPA should calculate the number of traffic fatalities that would result from the proposed plan. Traffic accidents also cause injuries. Under the same assumptions as above, EPA should predict the number of people that would be injured in traffic accidents due to their proposed actions.

#### Cancer and Respiratory Injury

The vast majority of automobiles, trucks and earth moving equipment are fueled either by gasoline or diesel fuel. In both cases, vehicle emissions are associated with adverse health effects. In addition to dioxins and furans, vehicles and construction equipment emit the known human carcinogen benzene, as well as many other substances that can cause harm, including polycyclic aromatic hydrocarbons, carbon monoxide, and nitrogen and sulfur oxides. Diesel vehicles emit many of these same

pollutants, but the EPA and other regulatory agencies have also designated diesel particulate matter (DPM), as a mixture, to be a potential human carcinogen (EPA 2002b). Many epidemiological studies of workers exposed to DPM have shown increased rates of lung cancer.

Gasoline fueled vehicles emit 12 to 473 mg of benzene per km traveled and 309 to 24,801 mg of total pollutants per km traveled (Schauer 2002). Diesel fueled vehicles emit 0.62 to 1.75 g of DPM per mile traveled (EPA 2002b). EPA should assess the vehicle pollution implications of its proposed toxicological criteria and calculate the number of tons of benzene, diesel particulate, carbon monoxide, sulfur oxides and nitrogen oxides that will be emitted into the air as a result of the additional dioxin site remediations that will be required because of the newly proposed toxicological criteria.

#### Emissions of Carbon Dioxide

Vehicles and construction equipment will emit carbon dioxide when investigations and remedial actions are undertaken if the PRGs were to be lowered as proposed. On average, passenger cars emit 0.92 pounds of carbon dioxide per mile, and light trucks emit 1.2 pounds per mile (EPA 2000c). It is unknown what effects this tonnage of *additional* carbon dioxide would have on global climate change, however, carbon dioxide emission *reductions* are being discussed at all levels of government, and EPA has embraced the concept of *green remediation*. Thus, EPA should assess the impacts of the proposed actions on global climate change.

#### Increased Traffic From Delivery of Remedial Construction Materials and Disposal of Waste

The proposed toxicological criteria in *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* also do not take into account the risks posed by vehicular traffic associated with the delivery of remedial construction materials and the disposal of dioxin containing waste.

#### Construction Injuries

Occupational injuries, illnesses, and death can occur during remedial construction projects. EPA should consult such statistics as those kept by the U.S. Department of Labor (2005) and estimate the number of occupational injuries, illnesses, and deaths that would result from implementing the EPA's proposed actions.

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