Journal of Toxicology and Environmental Health, Part B, 9:87–145, 2006

ISSN: 1093–7404 print / 1521–6950 online
DOI: 10.1080/10937400500538482

IDENTIFYING SOIL CLEANUP CRITERIA FOR DIOXINS IN URBAN RESIDENTIAL SOILS: HOW HAVE 20 YEARS OF RESEARCH AND RISK ASSESSMENT EXPERIENCE AFFECTED THE ANALYSIS?

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This article reviews the scientific evidence and methodologies that have been used to assess the risks posed by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and presents a probabilistic analysis for identifying virtually safe concentrations of TCDD toxicity equivalents (TEQ) in residential soils. Updated data distributions that consider state-of-the-science cancer and noncancer toxicity criteria, child soil ingestion and dermal uptake, bioavailability in soil, and residential exposure duration are incorporated. The probabilistic analysis shows that the most sensitive determinants of dose and risk are childhood soil ingestion, exposure duration, and the selected TCDD cancer potency factor. It also shows that the cancer risk at 1 per 100,000 predicted more conservative (lower) soil criteria values than did the noncancer hazard (e.g., developmental and reproductive effects). In this analysis, acceptable or tolerable soil dioxin concentrations (TCDD TEQ) ranged from 0.4 to 5.5 ppb at the 95th percentile for cancer potency factors from 9600 to 156,000 $(mg/kg/d)^{-1}$ with site-specific adjustments not included. Various possible soil guidelines based on cancer and noncancer risks are presented and discussed. In the main, the current toxicology, epidemiology, and exposure assessment data indicate that the historical 1 ppb TEQ soil guidance value remains a reasonable screening value for most residential sites. This analysis provides risk managers with a thorough and transparent methodology, as well as a comprehensive information base, for making informed decisions about selecting soil cleanup values for PCDD/Fs in urban residential settings.

A persistent and recurring issue in risk assessment is calculation of "acceptable" or "safe" levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other 2,3,7,8-chlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) in soil. Over the last 20 yr, numerous scientists have incorporated new information into risk assessments of residential soil to identify concentrations that limit or preclude concerns for health hazards to humans (DeRosa et al., 1997a, 1997b, 1999a, 1999b; Fields, 1998; Gough, 1988, 1991, 2003; Kimbrough et al., 1984; Paustenbach et al., 1986, 1992a, 1992b; U.S. EPA, 2003). Despite vigorous debate about the proper methodology, exposure factors, toxicity criteria, and a great deal of new information developed over the past decade, no one has attempted to bring all this information together to recommend a new soil guidance value (sometimes called a "cleanup value"). This article considers proposed methods and data, as well as the uncertainty in the toxicology and exposure data.

The methodologies used to conduct human health risk assessment and the science behind techniques to measure or estimate PCDD/F exposure and toxicity have evolved significantly since scientists from the U.S. Centers for Disease Control (CDC) developed their risk assessment for TCDD in residential soils (Kimbrough et al., 1984) and since our reanalysis of the CDC dioxin cleanup level for soils (Paustenbach et al., 1986). In 1978, Dow Chemical Company researchers published the results of a 2-yr cancer bioassay of TCDD showing a very high cancer potency in rats, thus raising concerns about the potential cancer risks to humans (Kociba et al., 1978). Since then, thousands of toxicological and epidemiological studies concerning TCDD and other PCDD/Fs have been published, and IARC (1997) and the National Toxicology Program (NTP, 2001) have categorized TCDD

This analysis was funded by the Dow Chemical Company, which has been studying PCDD/Fs for more than four decades. The firm has been and is currently involved in litigation related to PCDD/F contaminated soils. Each of the authors has researched the toxicology and risk assessment issues on dioxins for the past 10 to 25 yr and has provided consultations to various industrial, commercial, and governmental clients regarding the underlying science and presented their interpretations in academic, regulatory, and/or litigation settings. Dr. Paustenbach has been and continues to serve as an expert in dioxin litigation involving Dow Chemical Company.

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as a human carcinogen. Research on TCDD and other PCDD/Fs continues today at a robust pace. For example, the U.S. Environmental Protection Agency (U.S. EPA) recent "dioxin reassessment," which describes the agency's evaluation of the health risks posed by the PCDD/Fs, is nearly 2000 pages in length and cites nearly 1000 published papers (U.S. EPA, 2003).

Since the late 1970s, regular meetings of international groups of scientists from nearly every developed country have been convened to discuss the developing scientific evidence on TCDD exposure and toxicity (the 1986 Banbury Conference, and the annual International Symposium on Halogenated Environmental Organic Pollutants and POPs). Most recently, a new rodent cancer bioassay evaluating TCDD and 2,3,4,7,8-PeCDF has been completed (NTP, 2004) with alternative potency estimates made (Crouch et al., 2005; Faust & Ziese, 2004; Walker et al., 2005), tolerable intake estimates have been established by several groups (WHO, 2000, 2001; ECSCF, 2001; CoT, 2001), and several cancer potency estimates based on occupational epidemiology studies have been proposed (Crump et al., 2003; U.S. EPA, 2003; Aylward et al., 2005b; Starr, 2001; Becher et al., 1998; Steenland et al., 2001).

As recently as 1998, the U.S. EPA apparently supported the view that 1 ppb as determined by the CDC (Kimbrough et al., 1984) was a reasonable cleanup level for TCDD in residential soil (Fields, 1998). Specifically, the Office of Solid Waste and Emergency Response (OSWER) of U.S. EPA released directive 9200.4–26, which stated:

> Based on presently available information, and using standard default assumptions for reasonable maximum exposure scenarios, the upper-bound lifetime excess cancer risk from residential exposure to a concentration of 1 ppb dioxin is approximately 2.5×10^{-4}, which is at the higher end of the range of excess cancer risks that are generally acceptable at Superfund sites.

Details regarding the calculation of cancer risk were not provided in the directive, nor were noncarcinogenic risks presented. Table 1 summarizes soil cleanup standards for dioxin proposed by other regulatory agencies in the United States and abroad. Interestingly, cleanup standards based on the CDC 1 ppb action level have been criticized as a "policy-based level" that is inconsistent with U.S. EPA (1989b) risk assessment guidelines (Hirschhorn, 1997). The work by DeRosa and colleagues at

TABLE 1. Selected U.S. and International Residential Soil Criteria for TCDD Toxicity Equivalents (TEQ)

Country	Residential soil criteria	Comments/references
United States (U.S. EPA)	1000 ng TEQ/kg	U.S. EPA records of decision for Superfund sites, reviewed by Paustenbach et al. (1992b); Fields (1998)
United States (ATSDR)	1000 ng TEQ/kg	ATSDR (1997a, 1997b); DeRosa et al. (1999a, 1999b) action level
	50 ng TEQ/kg	Environmental Media Evaluation Guideline (EMEG) screening level excluding further investigation (ATSDR, 1997a, 1997b).
Texas	1000 ng TEQ/kg	Consistency with federal guidelines (Fields, 1998); promulgated value as part of Texas Risk Reduction Program
Michigan	90 ng TEQ/kg	Risk-based calculation (MDEQ, 2001)
Florida	7 ng TEQ/kg	Risk-based calculation; FDEP (2005), Chapter 62–777 (cleanup target levels)
Germany	1000 ng I-TEQ/kg	Action value set in 1999. Uses the 1990 WHO TEFs (BMU, 1999)
Japan	1000 ng TEQ/kg	Uses 1999 WHO TEFs (MoE, 2001)
New Zealand	1500 ng I-TEQ/kg	Set as an interim guideline, currently under review. Uses the 1998 WHO TEFs (MfE/MoH, 1997)
Canada	4 ng TEQ/kg	Derived from ambient background concentrations, is not effect-based; difficult to compare with others (CCME, 2001)
	Proposed Guidelines[a]	
Finland	500 ng I-TEQ/kg	Uses the 1990 WHO TEFs (AEA Technology, 1999)
The Netherlands	1000 ng I-TEQ/kg	Uses the 1990 WHO TEFs (AEA Technology, 1999)
Sweden	10 ng I-TEQ/kg	Uses the 1990 WHO TEFs (AEA Technology, 1999)

[a]The proposed guidelines are not legislative standards. The basis for their derivation is not stated, and details are not comprehensive. Thus, questions remain about the status of these guidelines.

the Agency for Toxic Substances and Disease Registry (ATSDR) was the last attempt to bring clarity to the issue (DeRosa et al., 1997a, 1997b, 1999a, 1999b; Pohl et al., 2002). Although the 1 ppb action level has been debated over the years, it remains an integral part of the guidance for dioxins detailed by ATSDR (1997a, 1997b).

The last two decades have seen an evolution in the risk characterization process (NAS, 1983, 1994, 1999; U.S. EPA, 1995b; Williams & Paustenbach, 2002). Risk assessments are now more transparent and present more rigorous evaluations of the data underlying the calculations than ever before. Indeed, in our view the methodologies approved by international groups like the World Health Organization (WHO, 2001), as well as the U.S. EPA (2003), regarding PCDD/F risk assessment serve as models for addressing public health concerns in the face of data gaps and uncertainties regarding the actual or potential human health effects of these compounds. However, neither of the risk assessments of PCDD/Fs in soil that have been published by CDC/ATSDR (DeRosa et al., 1997a, 1997b; Kimbrough et al., 1984), nor the OSWER directive (Fields, 1998), satisfies current expectations for transparency or uncertainty analysis, since it is not possible to reconstruct the derivation.

This risk assessment updates our previous work and analyses pertaining to the risk characterization of PCDD/Fs in soils (Paustenbach et al., 1986, 1992b). It attempts to account for the diversity of views about the toxicology of PCDD/Fs and about the many exposure factors that need to be considered when calculating soil guidance or cleanup criteria. The terms *cleanup criteria* and *soil guidance levels* must be used with caution, because the former may connote a legal requirement while the latter is perceived to be a general recommendation to risk managers. Based on our 20 yr of experience with this issue, risk managers and the public expect scientists to identify a concentration which is considered either "safe" or "unsafe." The definition of safety, of course, varies over time and with the circumstances (often influenced by the number of persons exposed, the severity of the adverse effect, etc.). Thus, even though some agencies offer general guidelines for public health officials to consider and apply such cleanup criteria on a case-by-case basis, this rarely occurs (for either practical, political, or legal reasons). In short, soil criteria offered by CDC/ATSDR, U.S. EPA, or similarly credible scientific bodies tend to be used broadly and without a serious evaluation of the scientific underpinnings.

In our view, it is not appropriate to develop or rely upon a generic soil cleanup level for PCDD/Fs; all soil criteria, including those described here, must be cautiously considered for their "fit" to the site-specific conditions. Any truly generic guideline must inherently be extremely low and would likely be associated with significant costs to society in terms of cleanup costs incurred and public fears fostered in the absence of objective benefit to public health. The "urban residential" criteria described here are suitable when site-specific considerations support no appreciable contribution from exposure pathways other than soil ingestion and dermal contact (e.g., no substantial continuing emission source and no substantial effect of the site soils on local fish, livestock, homegrown vegetables, or mother's milk). As explained in the Exposure Assessment section, we believe these additional pathways may be screened out for most sites where appreciable continuing emission sources of PCDD/Fs are absent. However, these indirect exposure pathways should be considered in any application of the soil cleanup criteria.

In the following sections we provide a detailed methodology and scientific basis to develop probability-based ranges for risk-based soil cleanup criteria applicable to PCDD/Fs in urban residential settings. Since our last paper (Paustenbach et al., 1992b) addressing soil cleanup levels for TCDD, new information has become available on factors that may dominate the risk calculations. These include new and better validated information on child soil ingestion rates, dermal uptake parameters, bioavailability, and residential exposure duration. Also, recent proposals on cancer potency factors and noncancer reference dose for TCDD have been evaluated. These different assumptions are incorporated using probabilistic techniques. Distributions of health risk-based PCDD/F soil clean-up levels consistent with U.S. EPA guidance were subsequently developed from these data (U.S. EPA, 1997b, 2001b). Our distributions for the various possible soil guidance values (and corresponding dose estimates) are compared to those adopted (or proposed) by public health agencies and other researchers in the United States and other countries. In this evaluation, the traditional risk assessment format as suggested by the National Academy of Sciences (NAS, 1983) is

followed, which includes hazard identification, dose response, exposure assessment, and risk characterization. Additionally, our analysis incorporates the use of probabilistic risk analysis techniques.

WHY USE A PROBABILISTIC RISK ANALYSIS?

The risk assessment process that became popular in the mid-1980s relied upon the use of single numerical values to predict the risk from exposure to chemicals. These so-called "point estimates" refer to the use of a single value for each risk parameter, resulting in a final estimate of risk that is also a single value. For example, saying that benzene exposure due to pumping gas during the 50 yr of adulthood poses an increased risk of leukemia of 1 in 10,000 is a point estimate. Risk distributions, on the other hand, refer to the use of a range of values for selected model parameters weighted by their likelihood of occurrence (U.S. EPA, 1997c). For example, exposure factors such as the amount of water ingested per day by the average person has often been characterized by the value of 2 L per day, although adults tend to drink between 1.2 and 2.5 L per day. For sake of simplicity, most assessors adopted the conservative (e.g., likely to overpredict the risk) value of 2 L per day. In contrast with a point estimate, the results from a probabilistic analysis might be, "Our estimate of the increased cancer risk due to pumping gas is that about 95% of the population who routinely fill their auto gas tank for 50 years should be at no greater risk of 1 in 100,000 assuming that they drive no more than 25,000 miles per year."

Not surprisingly, from about 1975 to 1995, most assessments were performed using a deterministic approach, and in nearly all cases, assessors repeatedly used a conservative value (e.g., one unlikely to underestimate the true number). This approach was justified because it ensured the inclusion of the maximally exposed person. Unfortunately, this methodology can lead to a phenomenon termed "compounding conservatism," which can predict risks that are unreasonably high (Burmaster & Harris, 1993; Nichols & Zeckhauser, 1988; Paustenbach, 1989). U.S. EPA (2004) recently addressed this topic in a comprehensive discussion document.

Fifteen years ago, we did not have the computing capability to consider distributions of possible risk values in our calculations but improved technologies have overcome this problem. Today, risk estimates can be calculated using probability-based techniques, such as Monte Carlo analysis, and can be presented as an entire probability distribution or for selected percentiles (e.g., 50th, 90th, 95th). However, even these risk assessments may not reflect all sources of variability and uncertainty. In particular, most evaluations have not incorporated the uncertainty in biologic parameters, such as cancer potency, which may be of much greater importance than the variability in most exposure parameters. In this assessment, that shortcoming is addressed.

There are many advantages to using stochastic (probabilistic) analysis in risk assessment, rather than the traditional point-estimate approach (Finley & Paustenbach, 1994). Primary among these advantages are;

- It eliminates debate over the "best" point estimate for an exposure parameter.
- It provides more realistic estimates of upper bound exposures.
- It provides detailed information on how risks are distributed based on population exposure.
- It tempers the influence of compounding conservatism.
- It gives the risk manager a more complete picture (e.g., transparency) regarding the factors which are driving the assessment, as well as the degree of uncertainty in the scientific underpinnings of the recommendation.
- It provides the information helpful to perform meaningful sensitivity and quantitative uncertainty analyses (Finley & Paustenbach, 1994; Finley et al., 1994; Williams & Paustenbach, 2002).

If necessary, scientific debates should resolve disagreements about the most appropriate data to be used in developing the probability density function (PDF) for a given exposure parameter. Often, these issues can be resolved by weighing each data set according to the quality of its data, and statistically combining the PDFs from different data sets into one PDF that represents the data from all sources (Finley et al., 1994; Paustenbach, 2000). Numerous papers presenting the PDF for

individual variables have been published in the risk assessment literature (Cohen et al., 1997; Burmaster, 1998, 1999; Burmaster & Crouch, 1997; Copeland et al., 1993, 1994; Finley et al., 1994; Smith et al., 1992; Stanek et al., 2001; U.S. EPA, 1997b), and the impact of the distributions on the outcome has also been discussed (Bukowski et al., 1995; Haas et al., 1997; Hamed & Bedient, 1997; Hattis & Burmaster, 1994; Hoffman & Hammonds, 1994).

In addition to exposure variables, cancer potency factors and reference doses are also amenable to probabilistic analysis where a robust database exists (Boyce, 1998; Evans et al., 1994a, 1994b; Shlyakhter et al., 1992; Sielken et al., 1995). As with exposure variables, the advantage to this approach is that it allows all reliable or high-quality data to be used (and weighted appropriately, where necessary), thus avoiding reliance on a single experiment or endpoint.

HAZARD IDENTIFICATION

Hazard identification is the process of evaluating the available toxicity studies and determining the range of toxic endpoints relevant to humans, as well as identifying any significant data gaps relating to the primary studies relied upon in the derivation of the toxicity criteria (e.g., cancer potency factor or reference dose) (reviewed in NAS, 1983, 1994).

Noncancer Hazard at Low Doses

There are dozens of studies that address the toxicology or epidemiology of TCDD and some dioxinlike compounds (Adami et al., 2000, 2001; ATSDR, 1998; DeRosa et al., 1999a, 1999b; Feeley & Brouwer, 2000; Greene et al., 2003; IARC, 1997; Kogevinas, 2001; Pohl et al., 2002; Smith & Lopipero, 2001; Starr, 2001; Sweeney & Mocarelli, 2000; U.S. EPA, 2003; WHO, 2001). Animal studies demonstrate a relatively diverse range of dose-dependent noncarcinogenic adverse responses to TCDD that vary considerably between species, including wasting syndrome, reproductive toxicity, developmental effects, and commonly observed toxic effects on the liver, kidney, gastrointestinal tract, and certain endocrine organs (ATSDR, 1998; U.S. EPA, 2003). Chloracne has been observed in studies of humans with excessive exposure to TCDD from occupational or accidental contact (Baccarelli et al., 2005; Caramaschi et al., 1981; Poland et al., 1971). Clinical tests have suggested subtle changes of metabolism, endocrine function, and developmental effects in humans (Bertazzi et al., 1998; Greene et al., 2003; Sweeney & Mocarelli, 2000), but such effects have not been conclusively demonstrated.

Research organizations, regulatory agencies, and individual scientists have relied on measures of different kinds of toxicity to determine "safe" exposure levels. In general, scientists examine the toxicolgic literature, pick out the adverse effect relevant to humans that occurs at the lowest dose, and calculate the risk of that adverse effect at various exposure levels. For instance, ATSDR scientists relied upon developmental studies in rodents and monkeys to set the agency's intermediate-duration and chronic minimal risk levels (MRLs). ATSDR relied upon immunological toxicity studies in guinea pigs (DeCaprio et al., 1986) for its intermediate MRL and developmental toxicity studies in monkeys (Schantz et al., 1992) for its chronic MRL. In a recent review of the TCDD literature concerning noncancer effects in animals and humans, Greene et al. (2003) identified chloracne in children exposed during the Seveso trichlorophenol reactor explosion incident (Assennato et al., 1989; Caramaschi et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986; Reggiani, 1978) as the best documented and lowest dose disease endpoint in humans. Greene et al. (2003) also identified developmental studies of TCDD as providing the best documented and lowest dose toxicity endpoint in animals (Faqi & Chahoud, 1998; Faqi et al., 1998; Gray et al., 1997a, 1997b; Mably et al., 1992a; Ohsako et al., 2001; Ostby et al., 1999). Scientists at the World Health Organization (WHO, 2000) and the Joint FAO/WHO Expert Committee on Food Additives (WHO, 2001) relied on these same developmental toxicity studies to derive their tolerable intake estimates for TCDD. These scientists, like Greene et al. (2003), believed their estimates of tolerable intake for the noncancer effects of TCDD would place the cancer hazard at negligible or tolerable levels (WHO, 2001). WHO (2001) identified tolerable estimates of intake for TEQ in the range of 1 to 5 pg/kg/d.

Interestingly, after a very long and exhaustive analysis, the United Nations working group on PCDD/Fs reached the conclusion that doses in the current Western diet should not be expected to produce adverse health effects (Renwick, 2004). The current average intake of dioxin/furan TEQ in the U.S. diet is about 1–3 pg/kg/d (U.S. EPA, 2003; WHO, 2001).

Cancer Hazard at Low Doses

TCDD has long been known as one of the most potent rodent carcinogens among the chemicals regulated by U.S. EPA. Different researchers and regulatory scientists have calculated the cancer potency of TCDD to range from 40 to 1,400,000 $(mg/kg/d)^{-1}$ based on findings from the same animal study by Kociba et al. (1978). This 2-yr cancer bioassay, which involved dietary ingestion of TCDD by rats, has been the basis for most of the published cancer potency estimates for TCDD and for the other 2,3,7,8-substituted PCDD/Fs (via the TCDD toxic equivalents approach) (van den Berg et al., 1998). Different interpretations of the data correspond to use of different assumptions about mechanism of action (e.g., nongenotoxic or genotoxic), endpoints to be modeled (e.g., neoplastic nodules vs. tumors vs. carcinomas), and extrapolation models (e.g., linearized multistage vs. safety factor approach) (Sielken, 1987). Recent developments include a further evaluation of cancer potency of TCDD and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in a chronic rodent bioassay (NTP, 2004), and proposals from U.S. EPA (2003) and others (Steenland et al., 2001; Becher et al., 1998) to rely on occupational cancer epidemiology studies to define PCDD/F cancer potency.

IARC (1997) evaluated the epidemiological literature on TCDD, noting the generally low magnitude of increased risk, the absence of any consistent pattern of site-specific cancer excess, and the lack of clear dose-response trends. The IARC workgroup classified TCDD as "carcinogenic to humans (Group 1)" based on this limited epidemiological evidence, sufficient animal evidence, and the fact that the presumed mechanism (Ah receptor activation) is known to occur in humans and experimental animals. However, a direct correlation between Ah receptor binding affinity and cancer response has not been clearly demonstrated in animals or humans for TCDD and other PCDD/Fs, and significant quantitative and qualitative differences between humans and animals almost certainly exist (Connor & Aylward, 2005).

The U.S. EPA Science Advisory Board (SAB) that reviewed the U.S. EPA "reassessment" in 2000 was fundamentally undecided about whether the available evidence was sufficient for TCDD to be considered a human carcinogen at any dose; at least half of the members concluded that the evidence was inadequate to support a "known human carcinogen" designation (Paustenbach, 2002b). This group within the SAB offered several lines of support for its views. One included an analysis that reported that only 2 of the 12 key cohort studies had significantly elevated total cancer mortality rates, and there was a flat dose-response trend (i.e., no dose-response relationship) when cancer rates were plotted against average body burden level for the various cohorts (Adami et al., 2000; Starr, 2001). Moreover, several groups of workers who had chloracne (which likely requires peak blood lipid TCDD levels above 5000 parts per trillion [ppt]; Greene et al., 2003) did not have increased cancer risk (Bodner et al., 2003).

Recent papers put into question the scientific foundation for U.S. EPA use of worker epidemiology studies to define its proposed TCDD cancer potency factor of 1,000,000 $(mg/kg/d)^{-1}$ (Aylward et al., 2005a, 2005b; Emond et al., 2004; Kerger et al., 2005a). Aylward et al. (2005a) showed (as others have suggested in the past) that the human half-life of TCDD is much shorter at high dose levels, based on a pharmacokinetic model of TCDD elimination in exposed Seveso residents and workers exposed to high levels of TCDD in a laboratory accident. This finding is significant because it invalidates the assumption in each of the epidemiology-based dose-response analyses that body burdens of workers can be calculated using a constant half life for TCDD. Aylward et al. (2005a) correctly note that if the TCDD half-life is shorter at high body burdens, determinations of dose based on calculations that incorporate a constant half life are underestimated (and potency is thereby overestimated). This has enormous implications in the derivation of a cancer slope factor from these occupational studies. Until the half-life issue is addressed for these occupational cohorts, in our view these cancer potency estimates based on dioxin epidemiology should not be used in quantitative risk assessment of TCDD.

PCDD/Fs are generally found in environmental media as chemical mixtures, and thus, humans are more likely exposed to mixtures rather than individual congeners. This is an obvious complication of the classic risk assessment paradigm because detailed dose-response studies are largely limited to TCDD. To address this challenge, toxicity equivalency factors (TEFs) were developed to facilitate the quantification of PCDD/F dose and potential health risks. TEFs are relative potency factors assigned to each dioxinlike chemical to approximate the total mixture potency relative to the well-studied and reasonably well-understood toxicity of TCDD in experimental animals. The process involves assigning individual TEFs to each of the 17 2,3,7,8-chlorinated congeners. There is a scientific consensus on the general mechanism through which these congeners begin to exert their effects; for example, they first bind with the Ah receptor in the cytosol of a cell, the receptor–ligand complex, then move to the nucleus of a cell where they bind to dioxin response elements in the regulatory portion of genes. This concept is reflected in the current regulatory approach, which relates the potency of other 2,3,7,8-substituted congeners to TCDD in comparable tests (TCDD, by definition, has a TEF of 1). The other 2,3,7,8-substitued congeners have TEF values ranging from 1 to 0.0001. Congeners without 2,3,7,8-substitution have been assigned TEF values of zero and are therefore not included in the analysis of TEQ. Despite a broad scientific consensus that use of this approach for risk assessment purposes is appropriate, there are substantial data gaps and scientific uncertainties associated with the use of the TEF approach (Finley et al., 2003; Safe, 1998) The specific values for the TEFs were to be reevaluated by the World Health Organization (WHO) in 2005 (WHO, 2005), and refinements to the 1998 WHO relative estimate of potency database and the use of a more quantitative TEF selection process have recently been proposed (Finley et al., 2003; Haws et al., 2004).

Although TCDD is the most widely studied of the PCDD/Fs, many studies have examined the toxicological properties of other congeners. The common underlying mechanism of action for all dioxinlike compounds is assumed to be that the chemical first binds to the Ah receptor (Portier, 2000; Safe, 2001; U.S. EPA, 2003; van den Berg et al., 1998). This assertion has been widely adopted for regulatory purposes to implicate all of the PCDD/Fs as multiorgan toxicants, even though the evidence remains limited as to whether or not the non-TCDD congeners exhibit the same broad range of effects as TCDD. For example, IARC (1997) concluded that there is sufficient evidence in animals and humans to designate TCDD as "carcinogenic to humans (Group 1)," while all other PCDDs and PCDFs are "not classifiable as to their carcinogenicity to humans (Group 3)." There is limited but growing evidence to support the assumption that other 2,3,7,8-substituted congeners have the capacity to cause the effects that have been documented in animals treated with TCDD (NTP, 2004; Walker et al., 2005; Starr, 2001; Starr et al., 1999; Yoshizawa et al., 2005). However, the receptor-mediated mechanism of action for TCDD is subject to competitive inhibition by other dioxinlike congeners as well as other environmental chemicals with varying degrees of Ah receptor affinity (Adami et al., 2000, 2001; Bannister et al., 1989, 1987; Biegel et al., 1989; Connor et al., 2004; Davis & Safe, 1989, 1990; Harper et al., 1995; Safe, 1998a, 1998b, 2001; Starr et al., 1999). The potential impact of such inhibition should not be discounted, especially at low environmental doses at issue for risk assessment.

Others have suggested that tumor rates below control levels in the lowest TCDD dose group of the Kociba et al. (1978) study may indicate competitive inhibition of TCDD-induced response and/or a hormetic effect, that is, depression of background cancer response at very low doses (Sielken & Stevenson, 1998; Calabrese, 2002; Calabrese & Baldwin, 2001a, 2001b; Paustenbach, 2002b). Thus, the net effect of the usual low-level exposure of humans to mixtures of dioxinlike compounds in the environment may present a much smaller human health hazard than that indicated by linear extrapolation models applied to animal studies of TCDD alone.

DOSE-RESPONSE ASSESSMENT

Dose-response assessment is the process of characterizing the relation between the dose of a chemical and the anticipated incidence of an adverse health effect in an exposed population. The bulk of our knowledge about the dose-response relationship at environmental PCDD/F concentrations is based on data collected from animal studies examining TCDD effects at doses several orders of magnitude higher, and on theoretical precepts about what might occur at these low environmental

doses in humans. This section is a discussion on the carcinogenic and noncarcinogenic toxicity criteria used in our analysis.

Cancer Potency

Health risks associated with exposure to carcinogens are stated as probabilities. These probabilities identify the likelihood of a carcinogenic response in an individual who receives a given dose of a particular compound. These probabilities are generally estimated using a cancer potency factor (CPF). The study by Kociba et al. (1978) was used by U.S. EPA to establish the original CPF of 156,000 $(mg/kg/d)^{-1}$ for TCDD. The CDC risk assessment by Kimbrough et al. (1984) derived slope factors based on the NTP (1982) and Kociba et al. (1978) rodent bioassays for TCDD that range from approximately 700 to 36,000 $(mg/kg/d)^{-1}$, and other agencies developed similar estimates prior to 1990 as summarized in Table 2.

The topic of an appropriate CPF for TCDD has been a subject of debate for many years. Table 2 illustrates the range of cancer potency values adopted by various regulatory agencies or researchers in the United States over the past two decades, including TCDD cancer potency estimates by Crouch et al. (2005) and Faust and Zeise (2004) based on the most recent bioassay (NTP, 2004). These cancer potency estimates were developed based on the assumption that TCDD follows a nonthreshold mechanism of carcinogenicity, despite the fact that the weight of scientific evidence indicates TCDD is not a genotoxic agent (Shu et al., 1987; WHO, 2001). Until recently, all of the cancer potency factors have been based on some kind of mathematical model applied to the rat bioassay conducted by Kociba and colleagues in 1978.

Sielken (1987) suggested that time to adverse effect is an important part of the risk assessment of TCDD. Sielken (1987) noted that the multistage model only utilizes quantal response data and thus does not consider time to response. The model proposed by Hartley and Sielken (1977) includes time to occurrence of carcinogenic response information. As described in this model, the mean free dose (MFD) is the dose level corresponding to a specified decrease in the mean response free period (Sielken, 1987). As noted by Sielken (1987), "A maximum allowable decrease in the mean response-free period can define a maximum allowable dose level (the mean free dose or MFD)."

Using time-to-response information from Kociba et al. (1978), Sielken (1987) calculated the virtually safe dose (VSD) and the MFD for a variety of time points using several different adverse effects (death from any cause, hepatocellular carcinoma, and hepatocellular neoplastic nodule or carcinoma). MFD estimated dose levels ranged from 0.6 to 7 ng/kg/d for time points ranging from a

TABLE 2. Summary of Model-Estimated Cancer Potency Factors (CPFs) for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Derived from Various Rodent Bioassays

Research group/key study and endpoints	Dose response extrapolation model	Cancer potency per (mg/kg/d)	Risk-specific dose at 10^{-6} (pg/kg/d)
U.S. FDA (1983): Kociba et al. (1978) total liver tumors in M/F rats	Linear interpolation	17,500	0.06
Kimbrough et al. (1984): NTP (1982) total liver tumors in M/F rats	Linearized multistage	700	1.4
Kimbrough et al. (1984): Kociba et al. (1978) total liver tumors in M/F rats	Linearized multistage	36,000	0.03
U.S. EPA (1985): Kociba et al. (1978) total liver tumors in F rats, including neoplastic nodules	Linearized multistage	156,000	0.006
Sielken (1987): Kociba et al. (1978) total liver tumors in F rats; mean response-free doses from 1000 to 5000 pg/kg/d.	Hartley–Sielken time-to-response	1.6 to 9.8	100–600
Sielken (1987): Kociba et al. (1978) and NTP (1980) total liver tumors in F rats.	Multistage fitted to the 3 lower doses	7 to 7.5	130–140
Crouch et al. (2005): NTP (2004) total liver, lung, gingival, uterine, and pancreatic tumors in female rats; 95% upper confidence limit potency estimate	Linearized multistage	16,000	0.06
Faust and Zeise (2005): NTP (2004) total liver, lung, gingival, uterine, and pancreatic tumors in female rats	Linearized multistage	26,300	0.04

1 d in a 70 yr reduction to a 1 mo in a 70 yr reduction. The VSD (which does not incorporate time to response) ranged from 0.07 to 0.60 ng/kg/d.

The high incidence of proliferative lesions (e.g., "hyperplastic nodules" or "neoplastic nodules") occurring in the livers of both treated and control rats in Kociba et al. (1978) resulted in a debate about how to classify these and other more subtle indicators of neoplastic change for the purposes of estimating cancer potency. In response, researchers from the National Toxicology Program (NTP) (Maronpot et al., 1986; McConnell et al., 1988) developed standardized criteria on this issue that represented a consensus among veterinary pathologists in the late 1970s (Squire, 1980; Squire & Leavitt, 1975). These revised NTP guidelines distinguish between hyperplasia, a nonneoplastic response to degenerative changes in the liver, and an adenoma, a benign condition involving clear differentiation of cells from the surrounding tissue (Maronpot et al., 1986).

In March 1990, a panel of seven independent pathologists, referred to as the Pathology Working Group (PWG, 1990a, 1990b), reevaluated the female rat liver slides from Kociba et al. (1978) and concluded that there were substantially fewer cancerous tumors (about two-thirds less) observed in the study than had been previously reported. The lesions previously identified as "hyperplastic nodules" or "neoplastic nodules" were reclassified as predominantly benign hepatocellular adenomas likely resulting from repeated hepatic cytotoxicity, since chromatid changes were not clearly evident. A summary of key differences in the incidence rates of liver tumors is provided in Table 3.

Several alternative estimates of TCDD cancer potency were developed following the PWG studies, all of which were lower than the original U.S. EPA (1985) cancer potency factor of 156,000 $(mg/kg/d)^{-1}$ (see Table 4). Paustenbach et al. (1991a) calculated the lowest CPF of 40 $(mg/kg/d)^{-1}$ by application of the Moolgavkar–Venzon–Knudson model (M-V-K model) to the Kociba et al. (1978) data (Moolgavkar, 1986; Moolgavkar et al., 1988; Moolgavkar & Knudson, 1981; Moolgavkar & Luebeck, 1990). Keenan et al. (1991) used the findings of the Pathology Work Group (PWG, 1990a, 1990b) and the linearized multistage model to derive upper bound cancer slope factors ranging from 2700 to 9600 $(mg/kg/d)^{-1}$ based on the incidence of heptocellular carcinomas alone or combined with liver adenomas, respectively. Goodman and Sauer (1992) using the same results and the same model derived an estimate of 51,000 $(mg/kg/d)^{-1}$ for liver tumors only, and 75,000 $(mg/kg/d)^{-1}$ for an increase in combined tumors of the liver, lung, or nasal turbinates/hard palate. The latter method avoids double-counting of tumor-bearing animals (U.S. EPA, 1995a).

In contrast to the Kociba et al. (1978) findings, a recently completed chronic rodent bioassay of TCDD and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (NTP, 2004) failed to reproduce the relatively high frequency of liver tumors from TCDD administration, and found a much lower cancer response for PeCDF than the one-tenth factor indicated by its WHO-TEF value (Walker et al.,

TABLE 3. Histopathological Interpretations of Hepatic Lesions in Female Sprague-Dawley Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Kociba et al. (1978) Bioassay: Original Findings Compared to Those Based on Updated Tumor Pathology Criteria (PWG, 1990a)

	Treatment dose (μg/kg/d)			
Study/endpoint	0	0.001	0.01	0.1
Kociba et al. (1978)				
Hepatocellular hyperplastic nodules	8/86 (9%)	3/50 (6%)	18/50 (36%)[a]	23/48 (48%)[a]
Hepatocellular carcinoma	1/86 (1%)	0/50 (0%)	2/50 (4%)	11/48 (23%)[a]
Total combined incidence	9/86 (10%)	3/50 (6%)	18/50 (36%)[a]	34/48 (71%)[a]
PWG (1990a)				
Hepatocellular carcinoma	0/86 (0%)	0/50 (0%)	0/50 (0%)	4/45 (9%)[a]
Hepatocellular adenoma	2/86 (2%)	1/50 (2%)	9/50 (18%)[a]	14/45 (31%)[a]
Total combined incidence	2/86 (2%)	1/50 (2%)	9/50 (18%)[a]	18/45 (40%)[a]

Note. Values given are number of responses/number of animals examined (percent response).

[a]Statistically significant difference ($p < .05$) from control by the Fisher exact text.

TABLE 4. Summary of Model-Estimated Cancer Potency Factor Estimates for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Based on the Revised Kociba et al. Pathology Data (PWG, 1990)

Research group	Endpoint(s) evaluated	Dose-response extrapolation model	Cancer potency per (mg/kg/d)	Risk-specific dose at 10^{-6} (pg/kg/d)
Paustenbach et al. (1991a)	Total liver carcinomas in F rats	M-V-K time to tumor	40	25
Keenan et al. (1991)	Total liver carcinomas in F rats	Linearized multistage	2700	0.37
	Total liver tumors (adenomas and carcinomas) in F rats	Linearized multistage	9600	0.10
Goodman and Sauer (1992)	Total tumors in liver (adenomas and carcinomas) in F rats	Linearized multistage	51,000	0.020
	Total tumors in liver, lungs, and nasal turbinates/hard palate in F rats	Linearized multistage	75,000	0.013
U.S. EPA (2000b)	Based on Goodman and Sauer (1992)	Benchmark dose 95% lower bound LED_{01}	1,100,000 to 1,400,000	0.0007 to 0.0009

2005). Crouch et al. (2005) estimated that the upper bound cancer potency for TCDD from this new NTP study is on the order of 16,000 $(mg/kg/d)^{-1}$, about an order of magnitude lower than the U.S. EPA (1985) estimate based on the Kociba et al. (1978) results. Similarly, Faust and Zeise (2004) estimated a TCDD potency of 26,300 $(mg/kg/d)^{-1}$ based on NTP (2004).

U.S. EPA (2003) asserts that benchmark dose modeling of body burdens (effective dose at 1%) from the Kociba et al. (1978) data (with the Goodman & Sauer [1992] pathology interpretations) corresponds to even higher upper bound cancer potency for TCDD, on the order of 1,100,000 to 1,400,000 $(mg/kg/d)^{-1}$ (see Table 4). The latter estimates based on linear extrapolation from the 95% lower bound benchmark dose (body burden) estimates are greatly influenced by choices to force fit the linear model from the highest dose data and through zero, rather than fitting the model to the significantly elevated tumor response data for lower doses as illustrated for the daily dose extrapolations by Sielken et al. (1987). The scientific integrity of these higher rat cancer potency estimates based on the Kociba et al. (1978) data is questionable, particularly in light of the recent TCDD bioassay findings (NTP, 2004; Crouch et al., 2005; Faust & Zeise, 2004). The NTP (2004) bioassay provides data on several lower doses, and better quality control with respect to quantifying TCDD levels in feed and in animal tissues, and with respect to avoiding potentially carcinogenic contaminants in test materials and feeds that may have influenced the Kociba et al. (1978) study.

Estimates of TCDD cancer potency based on occupational epidemiology studies are summarized in Table 5. Becher et al. (1998) were the first to provide such an estimate based on analysis of the Hamburg cohort, one of the smaller TCDD worker populations studied. Steenland et al. (2001) followed with an estimate for the much larger U.S. dioxin worker cohort by researchers of the National Institute for Occupational Safety and Health (NIOSH). U.S. EPA (2000, 2003) and Crump et al. (2003) used meta-analysis of the human epidemiology data from three studies as the basis for estimating a cancer potency factor for humans. Many scientists believe that the available epidemiologic evidence fails to demonstrate a genuine increase in human cancers that is attributable to TCDD because of the lack of consistency of the carcinogenic endpoint in humans, that is, no single tumor site or constellation of tumors (Paustenbach, 2002b; Starr, 2003; Starr et al., 1999). The animal and human evidence has been inadequate to define the carcinogenic potential of PCDD/Fs other than 2,3,7,8-TCDD (IARC, 1997), although a clear carcinogenic response was shown for 2,3,4,7,8-PeCDF in the recent NTP (2004) rodent bioassay. A recent weight-of-evidence review by Popp et al. (2005) concluded that there is strong support for a nonlinear, threshold-dependent, dose-response relationship for TCDD carcinogenicity. This may imply that background exposure levels carry a zero cancer risk and that force fitting the dose-response trends from high doses through the ordinate may be scientifically inappropriate for PCDD/Fs.

TABLE 5. Summary of Model-Estimated Cancer Potency Factors (CPFs) for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin from Occupational Epidemiology Studies

Reference citation and study details	Dose-response extrapolation model	cancer potency per (mg/kg/d)	Risk-specific dose at 10^{-6} (pg/kg/d)
Becher et al. (1998): (Hamburg Cohort). Additive linear model. Half-life value of 7.2 yr used to back-calculate serum TCDD correlated to excess risk for total cancers.	Linear extra risk of total cancers vs. cumulative serum lipid TCDD with constant half-life	2,200,000	0.00045
Steenland et al. (2001): (Updated NIOSH). Piecewise linear model. Half-life value of 8.7 yr used to back-calculate serum TCDD correlated to excess risk for total cancers.	Linear extra risk of total cancers vs. cumulative serum lipid TCDD with constant half-life	1,500,000	0.00077
U.S. EPA (2000, 2003): Meta-analysis: Fingerhut (1991) (old NIOSH), Ott and Zober, (1996) and Flesch-Janys et al. (1998). Half-life values ranging from 7.1 to 8.7 yr were used to back-calculate occupational body burdens correlated to excess risk for total cancers. Rounded mid-range potency for published and multiple internal model runs (ED-01) and 95% lower bound (LED-01).	Linear extra risk of total cancers vs. average body burden with constant half-life	1,000,000	0.001
Starr (2001): Meta analysis: Fingerhut (1991) (old NIOSH), Ott and Zober (1996), and Flesch-Janys et al. (1998). Half-life values ranging from 7.1 to 8.7 yr were used to back-calculate occupational body burdens correlated to extra risk for total cancers.	Linear extra risk of total cancers vs. average body burden with constant half-life	140,000 to 420,000	0.0024 to 0.0071
Crump et al. (2003): Meta-analysis: Steenland et al. (1999, 2001) (Updated NIOSH), Ott and Zober (1996), and Flesch-Janys et al. (1998). Half-life values ranging from 7.1 to 8.7 yr were used to back-calculate occupational body burdens correlated to extra risk for total cancers.	Linear extra risk of total cancers vs. cumulative serum lipid TCDD with constant half-life	222,000 to 400,000	0.0025 to 0.0045
Aylward et al. (2004, 2005b, 2005c): Steenland et al. (1999, 2001) (Updated NIOSH). Concentration and age-dependent half-life model (CADM) used to back-calculate occupational body burdens correlated to extra risk for total cancers.	Linear extra risk of total cancers vs. cumulative serum lipid TCDD and CADM half-life	10,000 to 250,000	0.004 to 0.10

U.S. EPA (2003) recommended that the cancer potency factor for TCDD should be raised from the current value of 156,000 $(mg/kg/d)^{-1}$, which was based on the Kociba et al. (1978) rat study, to a value of 1,000,000 $(mg/kg/d)^{-1}$ based on selected epidemiological data for cancer mortality among workers (Crump et al., 2003; U.S. EPA, 2003). Some researchers have argued that these same studies show that a threshold exists—that is, there is no increased risk below certain doses of the PCDD/Fs (Adami et al., 2000; Hays et al., 2001; Smith & Lopipero, 2001; Starr, 2001, 2003; Popp et al., 2005). The standard U.S. EPA approach of applying the linearized multistage model for defining upper bound cancer risks would be inappropriate for doses below such a threshold (Williams & Paustenbach, 2002).

ATSDR researchers have questioned the U.S. EPA view on its ability to predict the cancer risk at environmental doses using data from highly exposed human populations:

> U.S. EPA's reassessment of dioxin and related compounds may place too much confidence in the ability to accurately predict cancer risks at low doses. This approach dramatically increases cancer risk estimates that are not based on compelling new data but rather on the application of statistical models applied to results of occupationally exposed cohorts that have been associated with significant uncertainty regarding actual exposure. This is further confounded by the fact that these models are not yet fully validated and that we still have knowledge gaps with respect to the mechanism of action and interaction for the dioxin-like group of chemicals. (Pohl et al., 2002, p.)

Recently, the debate about how to mathematically interpret the epidemiology data has become more heated. The publications of Starr (2001, 2003), Crump (2003), and Aylward et al. (2004,

2005a, 2005b) clearly indicate that there is more than one approach that could be used, and the impact on the cancer potency factors can be dramatic (see Table 5).

For numerous reasons, in our view the CPF value of 1,000,000 $(mg/kg/d)^{-1}$ proposed by U.S. EPA is not sufficiently well grounded to consider in setting soil cleanup criteria. First, the pharmacokinetics upon which the peak body burdens of the workers in the epidemiology studies are based are almost certainly inaccurate, based on the work of Aylward et al. (2005a, 2005b) and others. Second, the debate between the biostatisticians who have examined these data sets highlights significant disagreement about whether the data show any relationship between body burden and an increased risk of cancer (Starr, 2001, 2003; Crump et al., 2003). Third, numerous epidemiologists and scientific bodies have raised serious questions about the reasonableness of assuming that the PCDD/Fs have the capacity to increase all tumors based on the human experience with dozens of other chemicals (Adami et al., 2000; Cole et al., 2003; Paustenbach, 2002b).

Furthermore, and as noted previously, Aylward et al. (2005a) have demonstrated that the half-life of TCDD in humans following exposure to high concentrations (e.g., >10,000 ppt in blood lipid) is less than originally thought (<3 yr). U.S. EPA researchers have identified similar concentration-dependent trends in the accidental TCDD poisoning incidents in Austria (Emond et al., 2004). Kerger et al. (2005a) recently evaluated body-burden data from Seveso residents who were under age 18 yr at the time of TCDD exposure and found half-lives averaging from 1.5 to 2.2 yr for individuals with the highest peak TCDD burdens and the most severe chloracne. Leung et al. (2005b) demonstrated similar concentration-dependent (lower) half-lives for penta-, hexa-, and heptachlorinated dibenzofurans in highly exposed Yucheng and Yusho patients involved in rice oil poisoning incidents. This new human evidence of concentration-dependent kinetics for PCDD/Fs has important implications for dose-response relationships, such as the epidemiology-based cancer slope factor of 1,000,000 $(mg/kg/d)^{-1}$ proposed by U.S. EPA (2003). This CPF is based on an assumed uniform TCDD half life of 7.5 yr; Aylward et al. (2004, 2005b) have estimated that concentration- and age-dependent pharmacokinetic models suggest the CPF is overstated by fourfold or more.

Regulatory agencies outside the United States have historically identified doses which they believe will reduce the cancer hazard to de minimus levels using a threshold-based approach. As shown in Table 6, all European countries and Canada in the 1980s and 1990s had adopted threshold-based approaches using the Kociba et al. (1978) data and safety factors to develop dose estimates of 1 to 10 pg/kg/d that were considered protective against carcinogenic effects of TCDD in humans. The U.S. EPAs concurrent approach using the linearized multistage model identified "safe" doses between 0.006 and 0.6 pg/kg/d based on predicted cancer risk levels of 1 in 10,000 to 1 in 1,000,000. As noted earlier, U.S. EPA (2000, 2003) proposed to raise their CPF estimate by nearly an order of magnitude by using body burden as the dose metric in a benchmark dose analysis applied to the Kociba et al. (1978) data.

More recently, the European Commission Scientific Committee on Food (ECSCF, 2001), the UK Committee on Toxicology (CoT, 2001), the World Health Organization (WHO, 2000), the Joint FAO/WHO Expert Committee on Food Additives (WHO, 2001), and others each provided an updated assessment of the literature and estimates of tolerable daily intake that are considered to be protective against both cancer and noncancer effects of TCDD (Table 7). The scientific rationale and calculations underlying the 1-pg/kg/d value were presented by Renwick (2004). In contrast, the U.S. EPA risk-specific dose (RsD, 1×10^{-6} lifetime cancer risk, 0.006 pg/kg/d) corresponding to the use of the cancer potency factor approach by regulatory agencies in the United States is one to three orders of magnitude lower than that implied by the tolerable intake estimates developed by these international scientific panels which have evaluated PCDD/Fs.

Noncancer Hazard Assessment

A number of different estimates of the so-called "safe dose" for noncancer effects have been published by regulatory agencies and other researchers over the past 20 yr concerning PCDD/Fs. Table 7 provides a summary of the noncancer toxicity criteria that have been published since 1983. The majority of these estimates fall in the range of 1 to 5 pg/kg/d.

TABLE 6. Procedures Used by Regulatory Agencies or Scientific Bodies to Estimate Virtually Safe or Tolerable Doses for Humans Based on Dose-Response Data from the Kociba et al. (1978) Chronic Cancer Bioassay for TCDD in Rats

Agency/group	Basis for extrapolation to humans	Results of extrapolation
The Netherlands, 1982 (Dutch State Institute of National Health, 1982)	Threshold, 250-fold safety factor on LOAEL of 1 ng/kg/d	Maximum daily intake of 4 pg/kg/d
Germany, 1985 (di Domenico, 1990)	Threshold, 100– to 1000-fold safety factor on NOAEL of 1 ng/kg/d	Maximum daily intake of 1–10 pg/kg/d
Swiss Institute of Toxicology, 1985 (Schlatter & Poiger, 1985)	Threshold, 100-fold safety factor applied to NOAEL of 1 ng/kg/d	Maximum tolerable daily intake of 10 pg/kg/d
United States, 1985 (U.S. EPA, 1985)	Nonthreshold, risk-specific dose for lifetime exposure at 10^{-4} to 10^{-6} excess cancer risk and TCDD potency of 156,000 per mg/kg/d	Risk-specific doses: 10^{-4} risk = 0.64 pg/kg/d 10^{-6} risk = 0.0064 pg/kg/d
Canada, 1985 (Ontario Ministry of the Environment, 1985)	Threshold, 100-fold safety factor applied to NOAEL of 1 ng/kg/d	Maximum allowable daily intake of 10 pg/kg/d
Denmark, 1987 (Ahlborg et al., 1988)	Threshold, 200-fold safety factor applied to LOAEL of 1 ng/kg/d	Maximum allowable daily intake of 5 pg/kg/d
United Kingdom, 1989 (United Kingdom, 1989)	Threshold, 1000-fold safety factor applied to NOAEL of 10 ng/kg/d	Allowable daily intake of 10 pg/kg/d
World Health Organization, 1990 (WHO, 1991)	Threshold, 100-fold safety factor applied to NOAEL of 1 ng/kg/d, including interspecies body burden analysis	Tolerable daily intake of 10 pg/kg/d
Japan, 1996 (cited in Larsen et al., 2000)	Threshold, 100-fold safety factor applied to NOAEL of 1 ng/kg/d	Allowable daily intake of 10 pg/kg/d
United States, 2000, 2003 (U.S. EPA, 2003)	Nonthreshold, risk-specific dose for lifetime exposure at 10^{-4} to 10^{-6} excess cancer risk and TCDD potency of 1,000,000 per mg/kg/d	Risk-specific doses: 10^{-4} risk = 0.1 pg/kg/d 10^{-6} risk = 0.001 pg/kg/d

U.S. EPA had previously established a noncancer reference dose (RfD) of 1 pg/kg/d for TCDD. This value was withdrawn in 1989 and has now been replaced with a "margin of exposure" approach that examines the source-related contribution to daily dose and/or body burden in comparison to background exposures and/or other no-effect level or low-effect-level dose benchmarks (U.S. EPA, 2000b, 2003). U.S. EPA currently asserts that an appropriately defined RfD for TCDD would be of no practical benefit because this "safe" dose would fall below background exposure levels (i.e., below daily intake in the foods of those in western society who have no unusual source of exposure) (Larsen et al., 2000). For example, based on Portier (2000), estimates of the effective TCDD dose (ED) at 1% effect incidence (ED_{01}) are as low as 0.013 pg/kg/d; this corresponds to a steady-state human body burden of 0.025 ng/kg (ng TCDD/kg body weight). Following a trend of decrease over the past two decades, current background human body burdens of TCDD appear to average around 3 ppt in blood lipid or about 0.75 ng/kg body weight for a 60-kg person with 25% body fat, with total lipid TEQ from PCDD/Fs being about 15 to 30 ppt TEQ (Aylward & Hays, 2002). U.S. EPA (2003) concludes it is not useful for risk assessment purposes to set an RfD that is well below average body burdens of TCDD and total TCDD toxic equivalents for the general public.

The issue of background dietary exposures becomes a potentially important concern for defining a proper noncancer toxicity criterion. The RfD criterion is defined as a safe dose level determined by taking a no-effect level or a low-effect level defined in human or animal studies and dividing that level by appropriate safety/uncertainty factors to arrive at a conservative level that can be compared to doses received from a particular source, for example, contaminated soils in a residential area.

U.S. EPA (2003) asserts that the low-effect levels observed in certain animal studies could plausibly occur at PCDD/F body burdens within 10- to 100-fold of the TEQ average in the background population. However, there is no confirmation that humans experience such effects, even in studies of humans with much higher body burdens. Several reviewers have pointed to the inconclusive nature of the studies that U.S. EPA (2000b) cited as evidence of human effects of PCDD/Fs at doses or body burdens near background levels (Bertazzi et al., 1998; Cole et al., 2003; DeRosa et al.,

TABLE 7. Procedures Used by Regulatory Agencies or Scientific Bodies to Estimate Virtually Safe or Tolerable Doses for Humans Based on Dose-Response Data for Noncancer Effects of TCDD

Agency/group	Basis for extrapolation to humans	Acceptable intake rate
Japan, 1983 (Larsen et al., 2000)	Yusho disease NOAEL in humans (1 ng/kg/day) with 10-fold safety factor for sensitive humans.	100 pg/kg/d
Germany, 1985 (Larsen et al., 2000)	Reproductive toxicity NOAEL = 1 ng/kg/d (Murray et al., 1979) with safety factor of 100 to 10000.	1 to 10 pg/kg/d
Nordic Group, 1987 (Ahlborg et al., 1988)	Reproductive toxicity NOAEL = 1 ng/kg/d (Murray et al., 1979) with safety factor of 100	10 pg/kg/d
United States, 1989 (U.S. EPA, 1989a)	Reproductive toxicity NOAEL = 1 ng/kg/d (Murray et al., 1979) with safety factor of 1000	RfD = 1 pg/kg/d
World Health Organization, 1990 (WHO, 1991)	Combined consideration of cancer, liver toxicity, reproductive and immune toxicity NOAELs = 1 ng/kg/d with 100-fold safety factor. Also adopted by UK, New Zealand, and the Netherlands.	10 pg/kg/d
United States, 1992 (ATSDR, 1992)	Reproductive toxicity NOAEL = 1 ng/kg/d (Murray et al., 1979) with 1000 safety factor for chronic/intermediate minimal risk level (MRL)	Chronic MRL = 1 pg/kg/d Intermediate MRL = 1 pg/kg/d
The Netherlands, 1996 (HCoN, 1996)	Reproductive toxicity LOAEL = 0.1 ng/kg-d in monkey studies with 100-fold safety factor	1 pg/kg/d
Japan, 1997 (EAJ, 1997)	Combined consideration of reproductive toxicity in monkeys (Rier et al., 1993) and carcinogenicity	5 pg/kg/d
ATSDR, 1998 (ATSDR, 1997a, 1997b; DeRosa et al., 1999a, 1999b)	Chronic MRL: Reproductive toxicity in monkeys with 120-fold safety factor applied to LOAEL (Schantz et al., 1992) Intermediate MRL: 90-d immunotoxicity study in guinea pigs with 30-fold saftey factor (DeCaprio et al., 1986).	Chronic MRL = 1 pg/kg/d Intermediate MRL = 20 pg/kg/d
U.S. EPA, 2000 (Portier, 2000)	ED-01 body burden of 0.025 ng/kg in rats based on Mably et al. (1992a) sperm effects, converted to human daily dose assuming 50% bioavailability and 7.6 yr half-life	0.013 pg/kg/d Margin of exposure approach: <0.1 pg/kg/d including background
World Health Organization, 2000 (WHO, 2000)	Reproductive toxicity in rats with 10-fold safety factor applied to LOAEL (Gray et al., 1997a, 1997b; Gehrs & Smialowicz, 1997; Gehrs et al., 1997) calculated from maternal body burden with half-life of 8.5 yr.	Tolerable daily intake: 1–4 pg/kg/d
European Commission, 2001 (ECSCF, 2001)	Reproductive toxicity in rats with 9.6-fold safety factor applied to NOAEL for male rat offspring (Faqi et al., 1998; Ohsako et al., 2001) calculated from maternal body burden with half-life of 7.6 yr.	Tolerable weekly intake: 14 pg/kg-wk or 2 pg/kg/d
United Kingdom, 2001 (CoT, 2001)	Reproductive toxicity in rats with 9.6-fold safety factor applied to NOAEL for male rat offspring (Faqi et al., 1998) calculated from maternal body burden with half life of 7.5 yr.	Tolerable daily intake: 2 pg/kg/d
World Health Organization (JECFA), 2001 (WHO, 2001)	Reproductive toxicity in rats with 9.6-fold safety factor applied to NOAEL for male rat offspring (Faqi et al., 1998; Ohsako et al., 2001) calculated from maternal body burden with 7.6 yr half-life.	Provisional tolerable monthly intake: 70 pg/kg-mo or 2.3 pg/kg/d

1999a, 1999b; Feeley & Brouwer, 2000; Greene et al., 2003; Kogevinas, 2001; Pohl et al., 2002; Starr, 2001; Sweeney & Mocarelli, 2000). The absence of findings confirming excess disease in humans at or near background body burdens may reflect the difficulties in finding proper control (unexposed) populations to distinguish them. However, it seems equally likely that, given the limited range of toxicity in humans at very high doses, alternative explanations may apply to risks at or near background body burdens of PCDD/Fs. These may include:

1. Humans may be less sensitive compared with test species in regards to experiencing the adverse effects under study.
2. The steady-state body burden of TCDD may not be an appropriate dose metric for comparisons between these animal studies and humans.

3. Studies of TCDD alone in animals may not be representative of the human population, which experiences predominant exposures to PCDD/F mixtures of which TCDD is only a small fraction (e.g., competitive inhibition of Ah receptor).
4. It may not be possible to extrapolate higher dose studies in animals to humans in a meaningful way because of a combination of factors that may include nonlinear (threshold-dependent) dose-response relationships, predominant influences of competitive inhibition of Ah receptor activation from environmental mixtures (Safe, 1998a), and/or hormetic effects of background environmental exposures in humans (Calabrese, 2002) that do not occur at higher/TCDD-only doses in animals.

Regardless of these considerations, U.S. EPA withdrew its original RfD of 1 pg/kg/d for TCDD and proposed a margin of exposure (MOE) approach as an alternative to evaluating noncancer risks. The MOE is calculated by dividing a "point of departure" for extrapolation purposes at the low end of the range of observation in human or animal studies (e.g., the ED_{01}) by the human exposure or body burden of interest (predicted dose). They propose that MOE values in excess of 100 to 1000 for background plus site-related TEQ doses "are adequate to rule out the likelihood of significant effects occurring in humans based on sensitive animal responses or results from epidemiologic studies." However, the practical application of this approach is hampered by many variables and uncertainties that will potentially take many years to sort out, including the reliable estimation of background exposures and the validity of many possible choices for the "point of departure" to be assessed (Aylward & Hays, 2002; Gaylor & Aylward, 2004; U.S. EPA SAB, 2001). Others have proposed that pharmacokinetic models similar to those used for risk assessment of lead exposures may be appropriate for dioxinlike compounds (Kerger et al., 2005b; Paustenbach et al., 2004). MOE analysis was not done in this assessment, and instead practical surrogate values for TCDD RfD were used to evaluate noncancer hazard.

International regulatory authorities have expressed noncancer toxicity criteria as tolerable daily intake (TDI) (WHO, 2000), tolerable weekly intake (TWI) (European Commission, 2001), or provisional tolerable monthly intake (PTMI) (WHO, 2001) expressed as a single value or a range (Table 7). These values are based on scientific panel reviews of the currently available literature on TCDD and other PCDD/Fs. These tolerable intake estimates are considered by these authorities to be protective against cancer and noncancer health effects of PCDD/Fs.

The ATSDR estimated safe dose for noncancer effects of TCDD considers duration of exposure. ATSDR has established acute, intermediate, and chronic minimal risk levels (MRLs). An MRL is defined as "an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer effects over a specified duration of exposure." The scientific basis for prior TCDD MRLs (ATSDR, 1992) and current MRLs (ATSDR, 1998) has been reviewed previously (DeRosa et al., 1999a, 1999b). The MRL values for acute (200 pg/kg-d) and intermediate (20 pg/kg-d) exposures are higher now (less conservative) than they were based on the available studies in ATSDR's earlier assessment (ATSDR, 1992). Indeed, the current MRL for intermediate oral exposures is 20-fold higher than the 1992 value, and the chronic MRL (1 pg/kg/d) remained consistent with the former chronic MRL and the former U.S. EPA reference dose for TCDD (U.S. EPA, 1989a). ATSDR explained that these MRL changes are the result of greater availability of human studies and animal studies that addressed certain uncertainties in the earlier MRL determinations (DeRosa et al., 1999a, 1999b). This reduced uncertainty translated into plausible justifications for the use of smaller safety margins on the MRL (DeRosa et al., 1999a, 1999b; Pohl et al., 2002).

One dose-response element that can be illustrated through the ATSDR MRLs for TCDD is the duration-dependent element that is expected for threshold-based noncancer effects of hazardous chemicals. When good quality human data are unavailable, the MRLs are derived for acute (1–14 d), intermediate (15–364 d), and chronic (365 d and longer) study durations and for the oral and inhalation routes of exposure in experimental animals. These standards are generally based on the most sensitive chemical-induced endpoint (with exposure durations within these guidelines) that is considered to be of relevance to humans. For example, the MRL for intermediate oral exposures is

based on a no-observable-adverse-effect level (NOAEL) for decreased thymus weight identified in the 90-d dietary exposure study of TCDD in weanling Hartley guinea pigs (DeCaprio et al., 1986). Effects on thymus weight and related immune parameters are highly sensitive indicators of TCDD toxicity in Ah-receptor-positive animals (ATSDR, 1998). Other intermediate-duration studies in rats, mice, and marmoset monkeys were cited by ATSDR in support of the use of this NOAEL (Kerkvliet, 1995; Madsen & Larson, 1989; Neubert et al., 1992; van Birgelen et al., 1995; Viluksela et al., 1994). It is important to consider that these studies of intermediate duration (15 to 364 d) in rodent life spans represent an equivalent time span of several years of exposure in the human life span. Thus, it seems reasonable to consider this intermediate oral MRL value as most relevant to intermediate-length exposure events like elevated soil ingestion during childhood. Uncertainty factors applied to the NOAEL included a factor of threefold for extrapolation from animals to humans, and 10-fold for human variability (ATSDR, 1998).

Shown in Table 8 are the RfD values proposed by Greene et al. (2003) that are based on a comprehensive review of the available literature on noncancer effects of TCDD through early 2003. These authors identified chloracne in humans and developmental/reproductive effects in animals as the only strong, consistent, and meaningful data upon which to base an RfD estimate for TCDD. They derived RfD estimates for both endpoints that were within the range of 1 to 6 pg/kg/d. Based on body-burden measurements of Seveso children with and without chloracne, they defined a lowest-observed-adverse-effect level (LOAEL) of 828 ppt in blood lipid. Greene et al. (2003) applied a 10-fold uncertainty factor for sensitive humans and used conservative pharmacokinetic modeling assumptions to arrive at an RfD estimate of 5 pg/kg/d. For the developmental/reproductive endpoints based on several TCDD studies in rats (Gray et al., 1997a, 1997b; Mably et al., 1992a, 1992b; Ohsako et al., 2001; Ostby et al., 1999), Greene et al. (2003) identified LOAEL and NOAEL values of 30 and 13 ng/kg maternal body burden, respectively, for adverse effects on sperm parameters and organ weights in the male offspring of treated rats. Using conservative pharmacokinetic modeling assumptions, they estimated a human equivalent NOAEL dose of 4 pg/kg/d. Based

TABLE 8. Procedures Used by Selected Independent Researchers to Estimate Virtually Safe or Tolerable Doses for Humans Based on Dose-Response Data for Noncancer Effects of TCDD

Researchers	Basis for extrapolation to humans	Acceptable intake rate
Greene et al., 2003 (independent U.S. researchers)	Human chloracne LOAEL for Seveso children with 10-fold safety factor (Mocarelli et al., 1991); body burden equivalence comparison and conservative back-calculation to daily dose.	Proposed RfD = 4 to 6 pg/kg/d
	Reproductive toxicity NOAEL with up to 3-fold safety factor (Ostby et al., 1999; Ohsako et al., 2001); same daily dose back-calculation.	Proposed RfD = 1 to 4 pg/kg/d Combined evidence point estimate: Proposed RfD = 5 pg/kg/d
Richter et al., 2006 (independent U.S. researchers)	Pharmacokinetic issues for TCDD in children: Seveso children TCDD half-life study supports concentration- and age-dependent model (CADM) of Aylward et al. (2005a) and 4-fold correction on Greene et al. (2003) proposed RfDs for shorter half life in children from ages 0 to 7.	CADM-corrected child RfDs based on Greene et al. (2003): For human data = 16 to 24 pg/kg/d For rodent data = 4 to 16 pg/kg/d Combined evidence point estimate Proposed child RfD = 20 pg/kg/d
Aylward et al., 2005c (independent U.S. researchers)	Pharmacokinetic issues for key rodent studies (Faqi et al., 1998; Ohsako et al., 2001) used to derive tolerable intake estimates: 2- to 3-fold lower TCDD transfer from mother to fetus due to chronic ingestion (Hurst et al., 2000a, 2000b; Chen et al., 2001) compared to the acute ingestion studies. Also 4-fold correction for lower transfer of non-TCDD congeners (Chen et al., 2001).	Ex: Implications for WHO (2000) Tolerable intakes: 1 to 4 pg/kg/d Changed by 8- to 12-fold: 8 to 24 pg/kg/d or 12 to 48 pg/kg/d

on the available human studies (e.g., Seveso, Italy), they concluded that the effects on male rat offspring occur at lower doses than any toxic effect observed in human study populations. Using the same key studies and different dosemetric evaluations, 3 other recent reviews derived tolerable intake estimates for TCDD in the range of 1 to 4 pg/kg/d (ECSCF, 2001; WHO, 2000, 2001).

Table 8 also provides some alternative values to consider for surrogate reference doses by considering some developing scientific issues. These issues are based largely on the manner in which dose-response extrapolations between animals and humans were used to derive the WHO (2000) TDI range of 1 to 4 pg/kg/d and similar estimates (CoT, 2001; ECSCF, 2001). Richter et al. (2006) note that by taking childhood pharmacokinetics into account, that is, the much lower and age-dependent half-life of TCDD observed in Seveso children and adolescents, it may be appropriate to apply a fourfold correction that raises the TDI range applicable to human children (ages 0 to 6 yr). This adjustment would raise the TDI for TCDD in children up to 4 to 16 pg/kg/d if the extrapolation is based on sensitive animal studies, and 16 to 24 pg/kg/d if based on the human chloracne response. Aylward et al. (2005c) also identified pharmacokinetic issues involved in the extrapolation of the sensitive animal reproductive toxicity data that would infer an 8- to 12-fold increase in the TDI range applicable to human adults. These findings lend further credibility to use of surrogate RfD values in the 10 to 20 pg/kg/d range as indicated in older estimates (Table 6).

EXPOSURE ASSESSMENT

Exposure assessment is the process by which the exposure of biological receptors to substances present in the environment is estimated and/or measured (Paustenbach, 2002a). Exposure assessment generally involves analysis of the following variables: (1) magnitude, rate or frequency, duration, and route of exposure; (2) nature and size of potential receptor populations; and (3) uncertainties associated with each variable (NAS, 1983). Exposure assessment is useful in identifying the optimal remedial alternative by estimating the likely human exposures associated with future land-use scenarios or remedial alternatives (Finley & Paustenbach, 1990; Paustenbach, 2000).

Exposure pathways are determined by environmental conditions (e.g., location of surface waters, groundwater, vegetative cover, prevailing wind direction, meteorologic factors), by the potential for chemical migration from one environmental medium (e.g., soil, water, or air) to another, and by the general activities of the potentially exposed populations (e.g., time spent inside or outside, level and type of work activity). Each pathway describes a unique mechanism by which a population or an individual may be exposed to a chemical. Although several potential pathways may exist, not all may be complete. For a pathway to be complete, the following conditions all must exist:

- A source and mechanism of chemical release to the environment.
- An environmental transport medium (e.g., air, water, soil).
- A point of potential human contact with the medium.
- A human exposure route at the contact point (e.g., inhalation, ingestion, dermal contact).

The potential for the occurrence of an adverse health effect associated with exposure to a chemical often depends on the rate and degree of systemic uptake (amount absorbed into the blood and tissues). For any route of exposure, the uptake (U) is the product of exposure (E) and the absorption efficiency, or bioavailability (B):

$$U = E \times B \tag{1}$$

Although a number of different factors are used to quantify exposure, the mathematical relation just shown holds true for all exposure routes and is expressed as mass of chemical per mass of body weight per day (mg/kg/d).

In this assessment, a health-based soil cleanup level distribution for an urban residential exposure scenario was derived using the TCDD toxicity criteria, PCDD/F TEFs, an acceptable level of risk

(theoretical excess cancer risk of 1×10^{-5} or hazard index of 1.0, as discussed further in this section), and measures of exposure and bioavailability. In essence, the calculation of a soil criterion is risk assessment in reverse, in which one begins with the acceptable level of risk and, through traditional risk assessment methodology and equations, derives the soil concentration (criterion) associated with the acceptable level of risk.

We identify the calculated criteria as modeling an "urban residential setting," which can be interpreted more broadly as any residential setting in which indirect TCDD accumulation pathways (breast milk, agricultural, and fish) can be ruled out as minor contributors relative to the direct soil contact pathways (dermal and ingestion). We infer that most urban and suburban residential environments will lack the site-related source elements that may validate concerns about accumulation through indirect pathways. For example, urban residential settings generally lack the source characteristics (i.e., substantial continued release of PCDD/F vapors, or substantial transport of soils to water sources) and/or the indirect pathway elements (such as large-scale agriculture, fisheries, or grazing and livestock raising practices) that provide a rationale for examining the doses and risks from these indirect accumulation pathways more carefully. It is necessary and important to carefully evaluate site-specific conditions to determine whether or not these indirect pathways are meaningful contributors to resident exposures before attempting to utilize the proposed soil cleanup criteria. Screening methods are available (e.g., U.S. EPA, 1998) to assess potential site-related impacts on these indirect pathways. Our intent is to inform the reader on leading indicators that in our experience can be used to rule out these indirect pathways as significant contributors compared to the direct soil contact pathways assessment.

Calculation of the urban residential scenario risk is generally considered to yield the lowest, most health-protective soil criterion when compared to industrial or commercial worker scenarios, or recreational use or trespasser scenarios. Each of the latter scenarios involves shorter exposure durations and less substantial cumulative soil ingestion exposures (the most sensitive exposure parameter) as compared to the residential child and adult exposure scenarios examined here. Accordingly, a soil criterion that is protective of urban residential exposures will be protective of other plausible urban resident, worker, or child exposure scenarios as well. As explained later, indirect exposure pathways (e.g., from homegrown produce, livestock, eggs, dairy products, or mother's milk) were not assessed in this risk assessment because these pathways are frequently absent or are not expected to appreciably contribute (e.g., $<5\%$ being a nominal influence based on professional judgment) to the estimated soil-related average daily dose in urban residential settings where past contamination of soils is the primary concern. However, if site-specific conditions indicate that these indirect exposure pathways (e.g., livestock or fish pathways) are substantial contributors to total risk, then these urban residential soil cleanup criteria may not be reasonable as a risk management tool.

For this urban residential scenario, potential exposures to both children and adults were addressed. Children have the potential for a greater dose due to higher intake rates (e.g., soil ingestion) and lower body weights, as compared to adults. This approach is consistent with U.S. EPA guidance (U.S. EPA, 1989, 1991).

Exposure Pathways Considered

Direct Contact: Soil Ingestion and Dermal Contact Because the PCDD/Fs are present in surface soil, direct-contact exposure pathways are considered potentially complete and were evaluated in this assessment. These pathways include incidental soil ingestion and dermal contact with soil.

Inhalation of Soil Dusts and PCDD/F Vapors From Soil Inhalation exposures due to PCDD/PCDF vapor release from soils and/or the suspension of surface soils in ambient air were not evaluated because these pathways are unlikely to contribute more than 1% to the total dose when compared to the direct-contact pathways (Paustenbach et al., 1991b). The extremely low vapor pressure of PCDD/Fs, combined with their tendency to adsorb to organic solids in soils, validates the assumption that airborne vapor exposure will be negligible from soils with low parts per billion levels, that is, up to 20 ppb (Paustenbach et al., 1991b). Further, groundcovers, including natural

groundcover, landscaping, and pavement (e.g., asphalt or concrete for paved roads and parking areas) in urban settings, limit both direct contact and inhalation exposures from impacted soils.

Homegrown Vegetable Ingestion Vegetable intake was not addressed in this analysis. The urban residential setting is assumed to have no significant ongoing emission sources of PCDD/Fs (otherwise, that would be the focus of a different assessment). Moreover, soil-bound PCDD/Fs are not incorporated into any substantial fraction of the edible plant material via the root system (U.S. EPA, 2003), and their low vapor pressure prevents substantial transport or uptake into aboveground vegetables (Lorber, 2001; Paustenbach et al., 1991b).

It is acknowledged that PCDD/Fs can sometimes be measured in certain vegetables, but the concentrations are always exceedingly low and the ultimate concentration in the processed foods (e.g., following cooking or peeling) will be insignificant and/or not measurable. It is also recognized that the *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (U.S. EPA, 1998) provides for the vegetable ingestion pathway, which is separated into calculations relevant to aboveground vegetables and belowground vegetables. For aboveground vegetables, the persistent presence of ground-level vapor emissions from an incinerator source is considered the primary contributor to potential plant uptake through leaves or exposed fruits and vegetables. Furthermore, extremely low vapor pressure of TCDD and other dioxinlike compounds prevents any substantial vapor flux from contaminated (and often long-weathered) soils (Paustenbach et al., 1991b). Lorber (2001) has suggested that the presence or absence of PCDD/Fs in vapor form dominates the home-grown vegetable/plant exposure pathways:

> The two primary pathways for the dioxin-like compounds to enter the ecological food chains and human diet are air-to-plant-to-animal and water/sediment-to-fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. Vapor phase transfers onto vegetation have been experimentally shown to dominate the air-to-plant pathway for the dioxin-like compounds, particularly for the lower chlorinated congeners. (p. 151)

In an urban residential setting with no continuing or substantial source of airborne PCDD/PCDF vapors, one can expect no appreciable air-to-plant transfer for homegrown aboveground vegetables. Similarly, the suspension of local soils with subsequent deposition on plants is also expected to be nominal for PCDD/F exposures via the home-grown vegetable pathway due to normal washing, processing, and/or cooking. Sheehan et al. (1991) provided calculations showing nominal contributions to total ingestion dose from soil-bound hexavalent chromium being deposited on homegrown vegetables (Sheehan et al., 1991), and one would expect similar behavior by PCDD/Fs.

Root vegetables (belowground vegetable pathway) in residential gardens must also be considered before excluding the vegetable pathway from the risk characterization in an urban setting. U.S. EPA (1998) guidance provides a methodology for calculating the partitioning of lipophilic chemicals like PCDD/Fs into certain types of root vegetables. However, such transfer of lipophilic chemicals from soils to root vegetables is shown to be primarily related to adhered soils as opposed to penetration into edible portions of the tuber (Cocucci et al., 1979; U.S. EPA, 2003; Wipf et al., 1982). For example, Wipf et al. (1982) grew carrots in soils containing 1 to 5 ppb of TCDD and reported that the concentration in the peeled, edible portion was only 0.75% of the surrounding soil TCDD concentration. This lack of appreciable uptake into edible portions of tubers is understandable from a physical/chemical partitioning standpoint because the tuber itself is generally rich in water content, a fact indicating that lipophilic chemicals will remain with soils or with the more lipid-rich root hairs or outer skin of the tuber. Similar considerations apply to vegetables grown on top of soil, like pumpkins and cucumbers (Muller et al., 1994; Hulster et al., 1994). Vegetables grown on top of soil have a limited surface area of direct contact with soil, and normal irrigation, vegetable washing, processing, and/or cooking are expected to further limit substantial ingestion of any transferred PCDD/Fs. Also, the process of soil amendment and tilling to prepare for growing vegetables is expected to reduce the surface soil concentrations of PCDD/Fs.

Homegrown Livestock, Dairy, and Poultry Products The incinerator risk assessment guidance (U.S. EPA, 1998) does not include exposures to locally grown livestock, dairy, or poultry products in

their assessment of residents living near a facility. Most urban areas have ordinances that prevent residents from raising livestock for consumption to avoid public health concerns that can arise from conducting such activities in more densely populated areas. Even if livestock were maintained in an urban residential setting, it seems unlikely that relevant application of the U.S. EPA (1998) guidance to residential exposures would lead to appreciable doses in the absence of persistent ground level PCDD/F vapor emissions.

The relatively high cumulative PCDD/F exposures to livestock and to "subsistence farmers" modeled in the U.S. EPA (1998) guidance are based on an assumed exposure period of 40 yr with dietary doses dominated by ingestion of 100% impacted homegrown livestock, dairy and poultry products. Each of these pathways, in turn, is dominated by persistent ground-level vapor emissions from the incinerator (and the air-to-plant transfer to grazing grasses, grains, and silage assumed to be regularly consumed by the livestock). Even if intermittent vapor emissions from soils occurred due to high ambient temperatures in summer, the steady-state-based calculations for these plant and animal accumulation pathways would not be applicable. Moreover, the expected frequency of homegrown livestock meals would be much lower in an urban residential setting compared to the subsistence farmer scenarios modeled for incinerator risk assessment (U.S. EPA, 1998).

Ingestion of Locally Caught Fish There is no doubt that in certain settings erosion of PCDD/F-containing soils can lead to their accumulation in sediments of water bodies. The modeling of potential accumulation of PCDD/Fs in fish is highly complex and site specific. Fortunately, regulatory safeguards have been implemented in most urban areas with known contamination sources to limit pollutant exposures via locally caught fish by placing bans or strict limits on fishing in such water bodies. It is also rarely the case that only one family of chemicals is at issue with respect to eating fish from polluted waters. Other persistent organic pollutants and heavy metals from unrelated sources and/or upstream regions are often at issue when it comes to evaluating the exposures and health risks from fish in polluted waters.

A limited evaluation regarding consumption of locally caught fish has previously been conducted (Paustenbach et al., 1992b). Paustenbach et al. (1992b) applied screening calculations regarding bioaccumulation in bottom-feeding fish using previously published methodologies (Cook et al., 1991; Goeden & Smith, 1989) and made a series of assumptions regarding erosion of impacted soils to a local stream using the universal soil loss equation in a generic watershed region. Age-specific fish consumption rates (0.49 to 1.48 g/d annual average based on per capita freshwater fish ingestion rate data, 210 d/yr) corresponded to lifetime average daily doses that were below 0.2% of that attributable to soil ingestion and dermal contact for a 30-yr residential exposure period (Paustenbach et al., 1992b). Courval et al. (1996) reported that 59% of U.S. recreational anglers consumed <12 fish meals per year and 84% consumed less than 24 fish meals per year. More conservative assumptions that might represent consumption rates of locally caught bottom-feeding fish for a recreational angler (e.g., six 8-ounce fish meals per year, 5.2 g/d and 210 d/yr) would still contribute less than 1% of the total dose under this modeled exposure (Paustenbach et al., 1992b). One must also consider that different species of fish that are eaten by recreational fishers may have a much lower bioaccumulation index compared to the bottom-feeding fish assumptions made in these modeled calculations.

Consumption of locally caught fish is not included in the U.S. EPA (1998) guidance for residents living near an incinerator. It is acknowledged that the fish ingestion pathway could be far more important than that modeled by Paustenbach et al. (1992b) in certain settings. However, one can also reasonably expect that many urban residential settings with PCDD/F-impacted soils have little or no significant soil-erosion-to-sediment transport pathway. Similarly, vapor and soil dust emissions are not likely to be significant contributors to water or sediment PCDD/F levels based on the preceding considerations discussed for the aboveground vegetable pathway. The incinerator risk assessment guidance (U.S. EPA, 1998) provides a methodology that is driven in large part by aerial deposition of incinerator stack emissions and secondary erosion from soils into sediments over a 30- to 40-yr time period, and assuming steady-state accumulation of PCDD/Fs in fish tissues. In urban settings where soil PCDD/Fs in noneroding areas are the primary concern, it is unlikely that relevant application of the U.S. EPA (1998) modeling procedures would predict fish accumulation that would result in substantial PCDD/F intake relevant to the soils as a source.

Breast Milk Exposures to Infants PCDD/F exposures to breast-fed infants are a potential concern because the PCDD/F body burden accumulated over the mother's lifetime partitions into the fat content of breast milk. This partitioning, combined with the relatively high fat content of breast milk and the high ingestion rate per body weight for young infants (e.g., 0 to 6 mo old) leads to calculated daily intake rates for PCDD/Fs that may exceed that from other dietary sources by one to two orders of magnitude. Such elevated exposure rates for breastfed children are not unique to PCDD/Fs, and apply to a variety of persistent lipophilic chemicals that are found in human adipose tissues.

The incinerator risk assessment guidance (U.S. EPA, 1998) recommends the calculation of potential incinerator-related PCDD/F intake by breast-fed infants. These calculations applied to a local resident near the incinerator are based on the assumption of regular exposures via inhalation and ingestion of homegrown vegetables and drinking water. In comparison to the subsistence farmer and subsistence fisher scenarios that include substantial bioaccumulation of PCDD/Fs in livestock or fish (via air-to-plant transfer and sediment accumulation pathways, respectively), the cumulative PCDD/F intake for urban residents from local soil ingestion and dermal contact is a negligible fraction of the mother's estimated body burden based on steady state accumulation assumptions.

The U.S. EPA (1998) breast-fed infant dose calculation method assumes that the breast-feeding mother has lived in the same location and accumulated exposure for the 30 yr preceding childbirth, and then breast-feeds her child for a full year, which in combination are highly unlikely to occur. In contrast, average residential duration is estimated at 9 yr. The steady-state calculations in the breast milk model are not adjusted properly for the limited fraction of the mother's body burden (versus other dietary source contributions in her lifespan before parturition) that could be plausibly related to the incinerator source.

Results from recent human studies indicate the half life of TCDD in infants (0.4 yr half-life) and young children through age 6 (0.5 to 2 yr half-life) is much shorter than the 7.5 to 11 yr value assumed for adults (Kreuzer et al., 1997a; Leung et al., 2005). Since the majority of PCDD/F dose from soils is related to childhood exposure assumptions, the shorter half-life in infants and young children equates with much lower body burdens (and hazard) than previously expected. Further, recent findings indicate that the half-life of TCDD increases at a gradual rate during childhood and adolescence, averaging less than 2 yr for individuals under age 18 (Kerger et al., 2005a). The shorter, age-dependent half-life is not incorporated into the U.S. EPA (1998) breast milk model, but infers much lower accumulation of PCDD/F in reproductive-age females, particularly considering the limited soil ingestion expected for adolescents and adults. These findings cast doubt on the validity of the breast-fed infant exposure model and its associated steady-state body burden calculations (Paustenbach et al., 2004). Improved pharmacokinetic models to assess breast milk and dietary PCDD/F exposures to children are being investigated (Kerger et al., 2005b; Paustenbach et al., 2004).

Probabilistic Risk Assessment Methodology

To better characterize the full range of potential exposures that could occur, a quantitative stochastic analysis was performed, using Latin Hypercube (LHC) statistics, to quantify the uncertainty and variability associated with the exposure parameters used to calculate the urban residential soil criterion. Latin Hypercube is a variant of the Monte Carlo sampling method that ensures selection of equal numbers of values from all segments of the distribution and divides the distribution into regions of equal sampling coverage. Hence, the values obtained will be forced to cover the entire distribution. It is more efficient than simple random sampling; that is, it requires fewer iterations to generate the distribution sufficiently (U.S. EPA, 2001b). The stochastic analysis used in this manuscript was prepared in accordance with the methods described in *Guiding Principles for Monte Carlo Analysis* (U.S. EPA, 1997b) and *Risk Assessment Guidance for Superfund: Volume 3 (Part A, Process for Conducting Probabilistic Risk Assessment)* (U.S. EPA, 2001b).

The U.S. EPA guidance recommends selecting the exposure pathways and chemicals that contribute the most to the risk/hazard from a deterministic or point-estimate analysis, and conducting the stochastic analysis only on those pathways that contribute significantly to the overall risk.

Dermal contact and soil ingestion, which are expected to contribute significantly to the overall dose, are evaluated in the stochastic analysis. In addition, use of the TEF methodology (van den Berg et al., 1998) relates the toxicity of all the PCDD/Fs congeners to that of TCDD. As a consequence, the assessment describes exposure to only one chemical in terms of PCDD/Fs (even though all 17 congeners are being evaluated).

A stochastic analysis involves only a few steps. In the first step of the analysis, the available data for each exposure parameter are evaluated with respect to distribution type (e.g., normal, lognormal, etc.), and the appropriate descriptors of the distribution (e.g., 50th percentile, mean, maximum, and minimum values) are determined. Commercially available software programs (e.g., @Risk, Crystal Ball) (Decisioneering, 2005; Palisade, 2005) then simulate a full distribution frequency for the parameter based on these descriptors. If only the range of values is known, a uniform distribution can be assigned to the exposure parameter. If only the range and mode are known, a triangular distribution may be most appropriate. It has been shown that one can usually characterize the data into one of these categories, and that using a less-than-perfect distribution has minimal impact on the results (Finley & Paustenbach, 1994; Finley et al., 1994).

Included in the last step of the stochastic analysis is a sensitivity analysis. The sensitivity analysis provides insight into which exposure parameter distributions have the greatest influence on the soil criterion. This analysis was performed to assist with risk management decision making, because it can be used to determine the relative importance of each exposure parameter distribution.

Calculation of Urban Residential Soil Criteria Based on Cancer Risk

The determination of a PCDD/F soil criterion is a three-step process. First, the target level of acceptable cancer risk is defined. Second, the exposure rate associated with this acceptable risk level is quantified using the exposure parameters for each route of uptake, and third, the soil criterion associated with the acceptable exposure rate is calculated.

The standard equation to calculate dose for each pathway is as follows:

$$\text{Dose} = \frac{\text{Soil Criterion} \times \text{CR} \times \text{EF} \times \text{ED} \times B \times \text{MET} \times \text{CF}}{\text{BW} \times \text{AT}} \tag{2}$$

where Soil Criterion is the concentration in soil (mg/kg), CR the contact rate (i.e., soil ingestion, mg/d), EF the exposure frequency (d/yr), ED the exposure duration (yr), B the bioavailability (unitless), MET the meteorological factor (unitless), CF the conversion factor (10^{-6} kg/mg), BW the body weight (kg), and AT the averaging time (d). Contact rate (CR) varies by exposure pathway. For soil ingestion exposures, it is the soil ingestion rate, or SIR (mg soil ingested/d). For dermal contact with soil, it is skin surface area, or SA (cm^2), multiplied by the daily soil-to-skin adherence factor, or AF (mg soil/cm^2 skin-d).

Rearranging the dose equation to solve for the acceptable concentration, or a PCDD/F soil criterion, yields:

$$\text{Soil Criterion} = \text{Dose} \times \left(\frac{\text{BW} \times \text{AT}}{\text{CR} \times \text{EF} \times \text{ED} \times B \times \text{MET} \times \text{CF}} \right) \tag{3}$$

The exposure parameters presented in Tables 9 through 12 and described in the following sections were used to estimate exposure in the dose equation for each pathway. The result is an "exposure factor" with units of kilograms of soil per kilogram body weight per day (kg/kg-d). The exposure factors (XFs) for each route of uptake were then combined with the appropriate dose-response criterion and target risk level to calculate the urban residential soil criterion, or the concentration in terms of PCDD/Fs in soil that will not likely exceed the target risk level.

TABLE 9. Exposure Parameters for the Child Scenario: Incidental Soil Ingestion

Parameter	Type	Value	Units	References
Soil ingestion rate[a]	Probabilistic	Empirical distribution: 25%ile = 11 50%ile = 24 75%ile = 41 90%ile = 73 95%ile = 88 Max = 137	mg/d	Stanek et al. (2001)
Exposure frequency[b]	Deterministic	350	d/yr	U.S. EPA (1991)
Exposure duration[c]	Probabilistic	Empirical distribution: 25%ile = 3 50%ile = 9 75%ile = 16 90%ile = 26 95%ile = 33 Max = 70	Yr	Johnson and Capel (1992)
Oral bioavailability	Probabilistic	Lognormal distribution: $\mu = 0.25$; $\sigma = 0.12$ Range: 0.005 to 0.63	Unitless	Ruby et al. (2002), Lucier et al. (1986), McConnell et al. (1984), Bonaccorsi et al. (1984), Shu et al. (1988), Umbreit et al. (1986)
Meteorological factor	Deterministic	1.0	Unitless	U.S. EPA (1991)
Body weight[d]	Probabilistic	Lognormal distribution: $\mu = 14.9$; $\sigma = 4.0$	kg	Finley et al. (1994)
Averaging time[e]	Deterministic	25,550	d	U.S. EPA (1991)

[a]An empirical distribution based on the percentiles of the child soil ingestion rates presented in Stanek et al. (2001) was used.
[b]Default value for the number of days per year that a resident may be present at home of 350 d/yr was used.
[c]An empirical distribution based on the percentiles of the residential occupancy data distribution presented in Johnson and Capel (1992) was used.
[d]The child body weight PDF developed by Finley et al (1994) from the analysis of the NHANES II data by Burmaster and Crouch (1997) for male and female children ages 0.5 to 6 yr was used.
[e]The default averaging time of 25,550 d (70 yr) was used.

Using XF to represent the exposure parameter portion of each pathway-specific equation yields:

$$\text{Soil Criterion} = \frac{\text{Dose}}{\text{XF}} \tag{4}$$

where

$$\text{XF} = \frac{\text{CR} \times \text{EF} \times \text{ED} \times B \times \text{MET} \times \text{CF}}{\text{BW} \times \text{AT}} \tag{5}$$

and Dose is the target "acceptable" dose at a 10^{-5} risk. In these equations, soil "criterion" is the acceptable concentration of PCDD/Fs calculated for soil (mg/kg).

For the calculation of the soil criterion, dose is defined as the daily intake of PCDD/F in terms of TEQs. The daily intake for a potentially carcinogenic chemical is defined by the following relation, in units of milligrams of chemical per kilogram of body weight per day (mg/kg/d):

$$\text{Dose} = \frac{\text{TR}}{\text{CPF}} \tag{6}$$

TABLE 10. Exposure Parameters for the Child Scenario: Dermal Contact With Soil

Parameter	Type	Value	Units	References
Skin surface area[a]	Probabilistic	Correlated with body weight	cm^2	Costeff (1966)
Fraction of skin attributable to body parts[b]	Deterministic	Hands—0.056 Forearms—0.13 Lower legs—0.24 Face—0.15 Feet—0.069	Unitless	U.S. EPA (2000a)
Soil adherence rate for different body parts[c]	Probabilistic	Lognormal distribution Hands—GM = 0.15 GSD = 2.10 Forearms—GM = 0.03 GSD = 1.80 Lower legs—GM = 0.02 GSD = 1.20 Face—GM = 0.06 GSD = 1.60 Feet—GM = 0.13 GSD = 1.40	mg/cm^2	Holmes et al. (1999)
Exposure frequency[d]	Deterministic	350	d/yr	U.S. EPA (1991)
Exposure duration[e]	Probabilistic	Empirical distribution: 25%ile = 3 50%ile = 9 75%ile = 16 90%ile = 26 95%ile = 33 Max = 70	yr	Johnson and Capel (1992)
Meteorological factor	Deterministic	1.0	Unitless	U.S. EPA (1991)
Dermal bioavailability	Probabilistic	Lognormal distribution: $\mu = 0.01$; $\sigma = 0.005$ Range: 0.001 to 0.025	Unitless	U.S. EPA (1992), Shu et al. (1988), Poiger and Schlatter (1980), Roy et al. (1990), Banks and Birnbaum (1991)
Body weight[f]	Probabilistic	Lognormal distribution: $\mu = 14.9$; $\sigma = 4.0$	kg	Finley et al. (1994)
Averaging time[g]	Deterministic	25,550	d	U.S. EPA (1991)

[a]Total skin surface area was set equal to a function of body weight with: Skin Surface Area (m^2) = [4 × (Body Weight (kg)) + 7]/[(Body Weight (kg)) + 90].

[b]The arithmetic mean fraction of total skin surface area represented by each body part for boys and girls 6 years and younger from U.S. EPA (2000a) was used

[c]Lognormal distributions based on geometric mean (GM) and geometric standard deviations (GSD) presented in Holmes et al. (1999).

[d]Default value for the number of days per year that a resident may be present at home of 350 d/yr was used.

[e]An empirical distribution based on the percentiles of the residential occupancy data distribution presented in Johnson and Capel (1992) was used.

[f]The child body weight PDF developed by Finley et al. (1994) from the analysis of the NHANES II data by Burmaster and Crouch (1997) for male and female children ages 0.5 to 6 yr was used.

[g]The default averaging time of 25,550 d (70 yr) was used.

where TR is the target risk level [1×10^{-5}] (unitless), and CPF is the cancer potency factor. Therefore, the following relation can be derived by combining Eq. (4) with Eq. (6) to derive a site-specific soil criterion for PCDD/F TEQs:

$$\text{Soil Criterion} = \frac{\text{TR}}{\text{CPF} \times \text{XF}} \tag{7}$$

TABLE 11. Exposure Parameters for the Adult Scenario: Incidental Soil Ingestion

Parameter	Type	Value	Units	References
Soil ingestion rate[a]	Probabilistic	Lognormal distribution: $\mu = 30$; $\sigma = 19.5$ Range = 10 to 100	mg/d	U.S. EPA (1997a); Calabrese et al. (1990, 1987); Stanek et al. (1997); Krablin (1989); Hawley (1985)
Exposure frequency[b]	Deterministic	350	d/yr	U.S. EPA (1991)
Exposure duration[c]	Probabilistic	Empirical distribution: 25%ile = 3 50%ile = 9 75%ile = 16 90%ile = 26 95%ile = 33 Max = 70	yr	Johnson and Capel (1992)
Oral bioavailability	Probabilistic	Lognormal distribution: $\mu = 0.25$; $\sigma = 0.12$ Range: 0.005 to 0.63	Unitless	Ruby et al. (2002); Lucier et al., (1986); McConnell et al. (1984); Bonaccorsi et al. (1984); Shu et al. (1988); Umbreit et al. (1986).
Meteorological factor	Deterministic	1.0	Unitless	U.S. EPA (1991)
Body weight[d]	Probabilistic	Lognormal distribution: $\mu = 71.0$; $\sigma = 15.9$	kg	Finley et al. (1994)
Averaging time[e]	Deterministic	25,550	d	U.S. EPA (1991)

[a] The U.S. EPA (1997a) default soil ingestion rate for adults in a residential scenario of 50 mg/d was used.
[b] Default value for the number of days per year that a resident may be present at home of 350 d/yr was used.
[c] An empirical distribution based on the percentiles of the residential occupancy data distribution presented in Johnson and Capel (1992) was used.
[d] The adult body weight PDF from Finley et al. (1994) based on the analysis of NHANES II data by Brainard and Burmaster (1992) was used.
[e] The default averaging time of 25,550 d (70 yr) was used.

Because there are two pathways of exposure contributing to the total dose, the soil criterion must be solved using the following equation:

$$\text{Soil Criterion} = \frac{\text{TR}}{\left[\left(\text{XF}_{\text{soil ingestion}} \times \text{CPF}_{\text{oral}}\right) + \left(\text{XF}_{\text{dermal}} \times \text{CPF}_{\text{oral}}\right)\right]} \tag{8}$$

Uptake via Soil Ingestion Pathway The uptake of soil via incidental ingestion was quantified for residential adults and children using the following equation:

$$\text{XF}_{\text{soil ingestion}} = \frac{\text{CR} \times \text{EF} \times \text{ED} \times B_{\text{oral}} \times \text{MET} \times \text{CF}}{\text{BW} \times \text{AT}} \tag{9}$$

where SIR is the soil ingestion rate (mg/d), EF the exposure frequency (d/yr), ED the exposure duration (yr), B_{oral} the oral bioavailability (unitless), MET the meteorological factor (unitless), CF the conversion factor (10^{-6} kg/mg), BW the body weight (kg), and AT the averaging time (d). The exposure parameters used to quantify the incidental soil ingestion XFs for children and adults are presented in Tables 9 and 11, respectively.

Uptake via Dermal Contact Pathway The following equation was used to calculate the XF for the dermal contact pathway.

$$\text{XF}_{\text{dermal contact}} = \frac{\text{SA} \times \text{BPF} \times \text{AF} \times B_{\text{dermal}} \times \text{EF} \times \text{ED} \times \text{CF} \times \text{MET}}{\text{BW} \times \text{AT}} \tag{10}$$

where SA is the total skin surface area (cm^2), BPF the body part fraction (unitless), AF the soil-to-skin adherence factor (mg/cm^2), B_{dermal} the dermal bioavailability (unitless), EF the exposure frequency (d/y),

TABLE 12. Exposure Parameters for the Adult Scenario: Dermal Contact With Soil

Parameter	Type	Value	Units	References
Skin surface area[a]	Probabilistic	Correlated with body weight	cm^2	Costeff (1966)
Fraction of skin attributable to body parts[b]	Deterministic	Hands—0.052 Forearms—0.059 Face—0.075 Lower legs—0.128 Feet—0.068	unitless	U.S. EPA (1997a)
Soil adherence rate for different body parts[c]	Probabilistic and deterministic	Lognormal distribution: Hands—GM = 0.20; GSD = 1.90 Forearms—GM = 0.05; GSD = 2.10 Lower legs—Point estimate = 0.072 Face—GM = 0.06; GSD = 1.60 Feet—Point estimate = 0.17	mg/cm^2	Holmes et al. (1999)
Exposure frequency[d]	Deterministic	350	d/yr	U.S. EPA (1991)
Exposure duration[e]	Probabilistic	Empirical distribution: 25%ile = 3 50%ile = 9 75%ile = 16 90%ile = 26 95%ile = 33 Max = 70	yr	Johnson and Capel (1992)
Meteorological factor	Deterministic	1.0	Unitless	U.S. EPA (1991)
Dermal bioavailability	Probabilistic	Lognormal Distribution $\mu = 0.01$; $\sigma = 0.005$ Range: 0.001 to 0.025	Unitless	U.S. EPA (1992); Shu et al. (1988); Poiger and Schlatter (1980); Roy et al. (1990); Banks and Birnbaum (1991)
Body weight[f]	Probabilistic	Lognormal Distribution $\mu = 71.0$; $\sigma = 15.9$	kg	Finley et al. (1994)
Averaging time[g]	Deterministic	25,550	d	U.S. EPA (1991)

[a] Total skin surface area was set equal to a function of body weight with: Skin Surface Area (m^2) = [4 × (Body Weight (kg)) + 7]/[(Body Weight (kg)) + 90].

[b] The arithmetic mean fraction of total skin surface area represented by each body part fro men and women from U.S. EPA (1997a) was used.

[c] Lognormal distributions based on geometric mean (GM) and geometric standard deviations (GSD) presented in Holmes et al. (1999).

[d] Default value for the number of days per year that a resident may be present at home of 350 d/yr was used.

[e] An empirical distribution based on the percentiles of the residential occupancy data distribution presented in Johnson and Capel was used.

[f] The adult body weight PDF from Finley et al. (1994) based on the analysis of NHANES II data by Brainard and Burmaster (1992) was used.

[g] The default averaging time of 25,550 d (70 yr) was used.

ED the exposure duration (y), CF the conversion factor (10^{-6} kg/mg), MET the meteorological factor (unitless), BW the body weight (kg), and AT the averaging time (d). The exposure parameters used to calculate the dermal contact XFs for children and adults are presented in Tables 10 and 12, respectively.

A probabilistic analysis requires the evaluation of available data regarding each exposure parameter to construct a PDF used in the analysis. Tables 9 through 12 present all input parameters and all of the PDFs used in the analysis. In addition, each PDF is briefly discussed in the following subsection.

Probability Density Functions for Cancer Risk Calculations

Sufficient data are available to build a PDF for the stochastic analysis for body weight, exposure duration, soil ingestion rate for children and adults, oral and dermal bioavailability, total skin surface

area, and soil-to-skin adherence factor. The remaining exposure parameters (i.e., percent skin surface area exposed, exposure frequency, meteorological factor, and averaging time) were input as single values (point estimates), because there are insufficient data available to describe the distribution of values. Tables 9 and 11 provide an overview of the exposure parameters and key references used for the child and adult soil ingestion dose calculations, respectively. Tables 10 and 12 provide an overview of the exposure parameters and key references used for the child and adult dose calculations for dermal contact, respectively. Further details on these selected parameters are described next.

Exposure Duration Johnson and Capel (1992) provide a listing of residential occupancy periods and associated percentiles. Data presented are based on individuals and represent the number of years from when an individual moved into a home until they either moved or died. The 50th percentile, 95th percentile, and mean of this distribution—9, 33, and 12 yr, respectively—generally agree with other estimates based on average current and total residence times and are quite similar to U.S. EPA-recommended default values for the average (9 yr) and upper bound (30 yr) exposures (U.S. EPA, 1997a). The distribution was truncated at a value of 70 yr and normalized, to be consistent with the lifetime used in the exposure factor calculation. Additionally, to ensure a level of conservatism, a lower bound value of 1 yr of residential exposure duration was used for all simulations.

For this analysis, the exposure duration must be attributed to time spent as a child or time spent as an adult, because different exposure assumptions apply to each. Because children have greater daily exposure potential than adults, exposure durations of 6 yr or less were assigned to the child's exposure assumption. Exposure durations of greater than 6 yr were assigned as 6 yr at child exposure assumptions, and the balance of the years was attributed to adult exposure assumptions.

Soil-to-Skin Adherence Factor To be consistent with U.S. EPA proposed guidance on assessing dermal exposures (U.S. EPA, 2001a), differences in soil-to-skin adherence factors for different parts of the body were addressed in this evaluation. The data from Holmes et al. (1999), as provided in the U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997a), were used to derive PDFs for each body part that can reasonably be anticipated to come into contact with affected soils. Data for the child age group (6 yr old or younger) with the highest soil adherence rate (Day Care Kids No. 1b) were used to ensure conservatism (Holmes et al., 1999). The distributions for soil adherence rates are different for various body parts of children and are each lognormally distributed. For hands, the distribution has a geometric mean of 0.15 mg/cm^2 and a standard deviation of 2.1 mg/cm^2; the values for the other body parts (e.g., forearms, face, lower legs, and feet) are presented in Table 10. Holmes et al. (1999) did not provide any estimates for soil adherence to the faces in this group. Therefore, the adherence rate reported for Gardeners No. 1 was used. This group had the highest facial soil adherence rates of all the groups studied, with the exception of those engaged in trench-digging activities (e.g., Utility Workers and Equipment Operators).

Adult adherence rates were lognormally distributed, and the group with the highest overall adherence rate and not engaged in trench-digging activities (Gardeners No. 1) from Holmes et al. (1999) were used (Table 12). For the hands, the geometric mean was 0.20 mg/cm^2, with a standard deviation of 1.9 mg/cm^2; the values for the other body parts (e.g., forearms and face) are shown in Appendix A. No PDF could be developed from the data in Holmes et al. for adult lower legs and feet, because of the limited number of data points for these body parts, and point estimates of 0.072 mg/cm^2 and 0.17 mg/cm^2 were used for the lower legs and feet, respectively.

Skin Surface Area The total skin surface area PDF was derived by correlating skin surface area to body weight. This correlation to body weight was accomplished by using the equation presented by Costeff (1966). The body weight/total skin surface area correlation was developed for use by physicians in need of a bedside formula to estimate skin surface area for medicinal purposes. It is appropriate to link physiologically correlated exposure parameters in a stochastic analysis to ensure realistic results. This correlation and other correlations of skin surface area to body weight and height have been previously evaluated (Murray & Burmaster, 1992).

Child Soil Ingestion Rate Incidental soil ingestion is one of many pathways of exposure to environmental chemicals, and frequently contributes most significantly to the total estimated dose of chemicals in soil (Paustenbach, 1989, 2000). While working or playing outdoors, children and adults may accumulate soil on their hands, and then, through hand-to-mouth contact, ingest

it. Children less than 6 yr old have a tendency to place their hands and other objects into their mouths more frequently than do older children and adults. This mouthing behavior results in higher incidental soil ingestion rates among children than among adults and, in conjunction with a smaller body weight, results in a relatively greater estimated dose of chemicals in soil. As a consequence, most soil ingestion studies have focused on children, although a few small studies have been conducted on adult volunteers (Calabrese et al., 1990; Stanek et al., 1997). A detailed overview on the available soil ingestion rate studies in children is presented here because this parameter has a dominant influence on the risk-specific dose and cleanup level calculations in the current study.

Historically, U.S. EPA has recommended an upper bound value for soil ingestion of 200 mg/d for children and 100 mg/d for adults for use in health risk assessment (U.S. EPA, 1991). However, U.S. EPA (1997a, 2000a) recommends 100 mg/d as the best estimate of the mean long-term soil ingestion for children and states that 200 mg/d may be used as a conservative upper bound estimate of the mean. U.S. EPA (2000a) reached these conclusions based on review of the mean values from the soil ingestion studies, noting that most reported values were below the 200 mg/d value used previously. Furthermore, U.S. EPA found that the mean soil ingestion rate across all of the studies reviewed was 138 mg/d, that the highest values were observed using titanium as a fecal tracer, which tends to exhibit great variability, and that one study measured soil ingestion for a child displaying pica at the time of the investigation (U.S. EPA, 1997a). U.S. EPA concluded, based on its review of all available data, that 100 mg/d is the best estimate of mean soil ingestion among young children.

Our review of the literature indicates that the study published by Stanek et al. (2001) provides the most robust data set on which to base a PDF for the stochastic analysis. This distribution represents an estimate of long-term average soil ingestion rates based on daily soil ingestion estimates from children who participated in a mass-balance study in Anaconda, MT. The resulting soil ingestion estimate is represented by a cumulative distribution with a median value of 24 mg/d, a 95th percentile of 91 mg/d, and a maximum of 137 mg/day (Stanek et al., 2001). The authors state on page 361 of the published study, "The results [from this study] provide what we consider to be the best characterization to date of the distribution of daily soil ingestion for children." Figure 1 provides both the cumulative frequency distribution and PDF used in the stochastic analysis for this parameter.

Prior studies of child soil ingestion rates, including earlier studies by Calabrese and colleagues, have reported data distributions with highly variable ingestion rates that exceed those observed by Stanek et al. (2001). Studies conducted in the early 1980s relied on observations of personal hygiene and hand-to-mouth habits to derive child soil ingestion estimates (Brunekreef et al., 1983; Lipsky, 1989; Paustenbach, 1987). For example, based on interviews with pediatricians and other professionals, Kimbrough et al. (1984) assumed that as much as 10,000 mg/d of soil could be ingested by children between the ages of 1.5 and 3.4 yr, and that children between 3.5 and 5 yr old may ingest up to 1000 mg/d. Since then, more sophisticated direct measurement methods have been developed to collect data on soil ingestion rates using nonmetabolizable soil trace elements in feces and urine (Binder et al., 1986; Calabrese et al., 1989a, 1989b, 1990; Clausing et al., 1987; Davis et al., 1990; van Wijnen et al., 1990). These studies identified soil ingestion rates in children in the range of 5 to 200 mg/d, but did not rigorously address mass balance problems commonly found in each of these data sets.

The presence of trace elements in some foods, however, appears to be responsible for mass balance problems and the apparent wide range of soil ingestion rates reported among children (Binder et al., 1986; Calabrese et al., 1989a, 1989b). An evaluation of soil recovery variances and soil detection limits for various tracers across the four major studies then available (Binder et al., 1986; Calabrese et al., 1989a, 1989b; Davis et al., 1990; van Wijnen et al., 1990) was conducted and it was concluded that soil ingestion rates of 16 to 55 mg/d were the most statistically reliable estimates (Calabrese & Stanek, 1991; Stanek & Calabrese, 1991). The median value of 24 mg/d reported by Stanek et al. (2001) is consistent with these conclusions from over a decade ago.

A mass balance-based soil ingestion rate study on 64 children, ages 1 to 4 yr, assessed potential exposure to arsenic in soils for residents living on a Superfund site in Anaconda, Montana (Calabrese

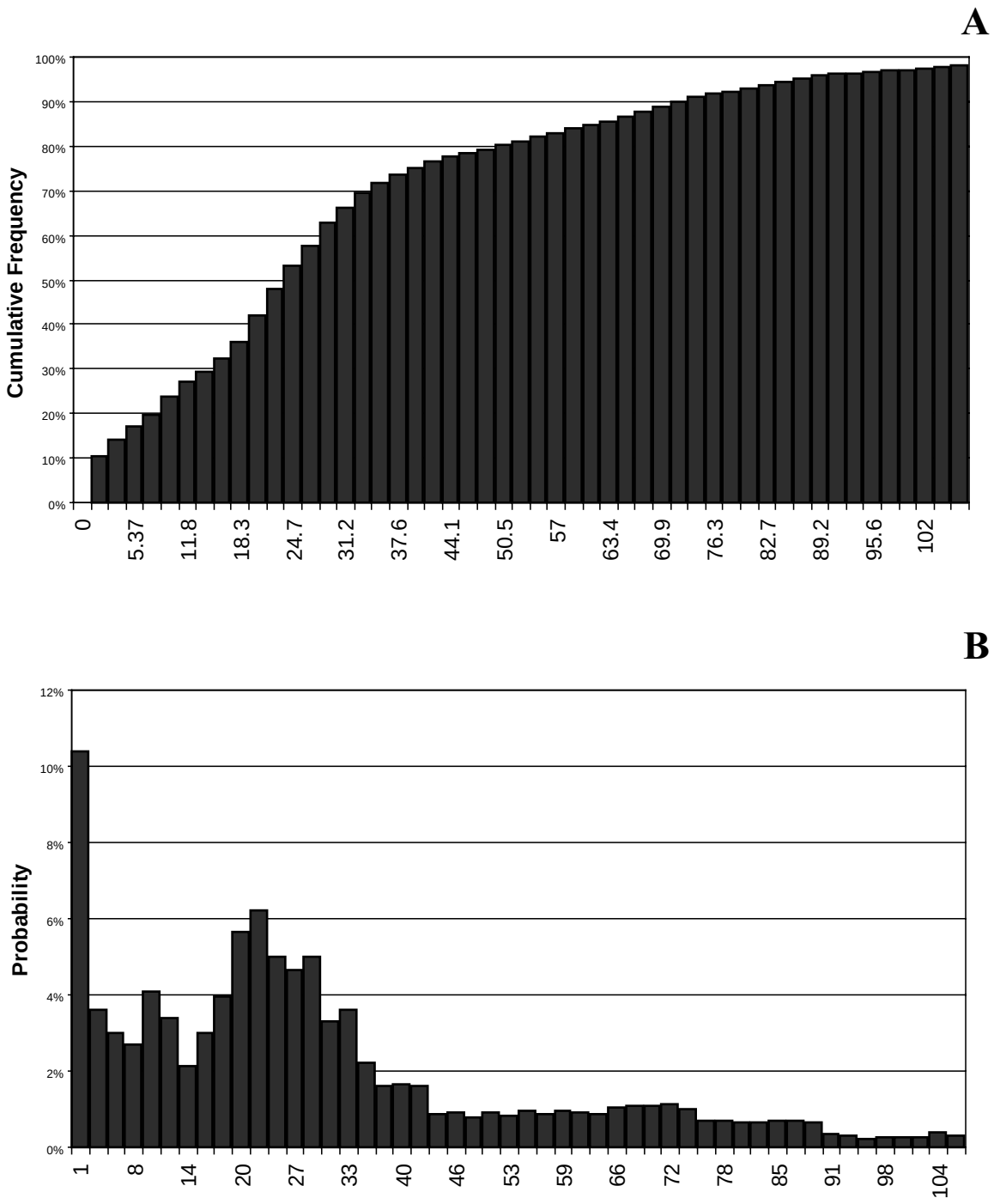

FIGURE 1. (A) Cumulative distribution and (B) probability density function (Panel B) of child soil ingestion rates (mg/d) used for exposure assessment. Note that about 95% of children were found to consume less than 100 mg/d (ages 0–6 yr).

et al., 1997b; Stanek et al., 1997). These authors used the best tracer method (BTM) to correct for errors in tracer input and output measurements and error from ingestion of these tracers from non-food and nonsoil sources. An additional benefit of the BTM is that it is not dependent on soil or dust

particle size measurements. Al, Si, Ti, Y, and Zr were the five best tracer elements, because they had relatively uniform soil concentrations across particle size. Using these tracers, the median soil ingestion rate was less than 1 mg/d, and the 95th percentile was 160 mg/d. The authors discuss the possibility of residual negative error that would occur more often than residual positive error. The net effect of the former would result in the soil ingestion estimates being less than the true soil ingestion rate. One final note by the authors indicates that soil ingestion rates may be lower for this study population, as compared with other populations, because the parents were aware that they lived on an active Superfund site and may have been more diligent in ensuring that their children did not contact and ingest soil.

Stanek and Calabrese (2000) published a reanalysis of the just described study of Anaconda, MT, children. This reanalysis estimated daily soil ingestion rates, which were used to estimate the distribution of 7-d average soil ingestion rates over different time periods (i.e., 30, 90, and 365 d). In short, this analysis provides a method for extrapolation of short-term data to long-term estimates for use in health risk assessments. Average daily soil ingestion estimates over the 7-d period for each child in this study were calculated according to the procedures used by Stanek and Calabrese (1995) and Calabrese and Stanek (1995). The mean and median of the 7-d average ingestion rates for all subjects in this study were 31 mg/d and 17 mg/d, respectively, with a 95th percentile of 141 mg/d. Of note is the highest weekly average daily soil ingestion rate by 1 subject (173 mg/d), which was due to ingestion of 600 to 700 mg soil on the last day of the study, suggesting pica behavior.

Stanek and Calabrese (2000) used the 7-d average soil ingestion rate to estimate long-term soil ingestion rates. As the authors state, the distribution of the true long-term average soil ingestion rates should be much narrower than the distribution of estimated rates based on short-term data because of regression to the mean. To account for this phenomenon, the study details the mathematical formula used to estimate this effect based on variance and uncertainty derived after various outliers were removed from the data [i.e., the soil ingestion estimates based on Ti were considered outliers based on Tukey's criteria (Tukey, 1977) and were eliminated]. Such calculations resulted in long-term 95th percentile estimates of 143 mg/d over 7 d, 123 mg/d over 30 d, 119 mg/d over 90 d, and 117 mg/d over 1 yr. These results compare well with those obtained from a previous study of children in Amherst, MA, in which Calabrese et al. (1989a, 1989b) determined 95th percentile soil ingestion rates of 177 mg/d over 7 d, 135 mg/d over 30 d, 127 mg/d over 90 d, and 124 mg/d over 1 yr. This agreement between the Amherst and Anaconda data sets was observed despite the fact that the parents in the Anaconda study knew that they lived on an active Superfund site. This finding indicates that parents' instructions to children not to get dirty or put things in their mouths had little effect on the soil ingestion rate estimates.

Stanek et al. (2001) published another statistical reanalysis of their previous mass balance soil ingestion studies that was focused on providing reliable data for probabilistic risk analysis. They used the "best linear unbiased predictors" (BLUP) method (Stanek et al., 1999), with the observed median ingestion rates, to estimate soil ingestion per subject-day. The median was used, as opposed to the mean, because the median value is more robust from these types of studies for each subject-day. In addition, the median is less sensitive to trace-element biases due to source error or systemic absorption differences that may occur with the individual tracer elements. The first step of the analysis was to test the Anaconda data for potentially unreliable soil ingestion estimates based on individual tracer elements. This was accomplished by examining the distribution of the variance of median soil ingestion estimates, using small sample estimates of the variance. The variance of the median soil ingestion rate on a given subject-day was calculated using all but one tracer. This was performed iteratively by omitting each possible tracer element in succession. This technique indicated that soil ingestion estimates based on the Ti tracer were unreliable. Consequently, this tracer was omitted from all subsequent analyses.

Stanek et al. (2001) used what they termed a "bootstrap approach" to estimate daily soil ingestion for each subject, using the median daily soil ingestion rate data for multiple tracer elements each day, and the estimated variance of the median. Tracer element-specific soil ingestion rate estimates on a subject-day were simulated with a normal distribution. The parameters for this method were set such that the expected value of the tracer element estimate corresponded to the observed median soil ingestion, and the standard error average of the tracer element estimates corresponded

to the standard deviation of the median (Stanek et al., 2001). With this method, the authors conclude that the average of the tracer element-specific estimates for each subject-day provide an unbiased estimate of the median and the variance (Stanek et al., 2001).

The resulting distribution provides an estimate of the long-term average soil ingestion rate based on daily soil ingestion estimates for children who participated in the Anaconda study. The resulting soil ingestion rate estimate is represented by a cumulative distribution with a median value of 24 mg/d and a 95th percentile value of 91 mg/d (see Table 1 in Stanek et al., 2001). These results were used to support a stochastic analysis in our probabilistic assessment of soil dioxin TEQ cleanup levels in an urban residential setting.

When comparing the results of different soil ingestion studies, it is important to recognize that only three mass balance studies have been conducted to date (Calabrese et al., 1989a, 1989b, 1997b; Davis et al., 1990; Stanek et al., 1997). The other studies suffer from limitations, including input/output alignment errors and not considering the particle size distribution of ingested soil, which result in inaccurate conclusions about soil ingestion (Calabrese et al., 1996). However, the protocol used in this series of studies (Calabrese et al., 1996, 1997b; Stanek et al., 1997) and the subsequent statistical analysis of Stanek et al. (2001) and Stanek and Calabrese (2000) are vastly improved over those used by previous researchers and, as such, represent the most accurate estimates of soil ingestion rate distributions to date. Therefore, it is important to consider how the refinements incorporated by Stanek et al. (2001) produce lower estimates of soil ingestion than those previously reported and recommended by the U.S. EPA (1997a, 2000a).

Numerous studies of soil ingestion in children are available, and many of these articles account for some of the recognized biases or limitations of soil ingestion estimates. However, Stanek et al. (2001) took advantage of the evolving knowledge on this issue, and the potential biases, to develop a distribution of soil ingestion rates for children. Specifically, the authors accounted for the application of short-term study data to represent long-term exposure, accounted for the particle size of the ingested soil, used the median tracer element estimate for subject days, accounted for the small sample variance of the median estimates, and used best linear unbiased predictors to estimate the cumulative long-term soil ingestion distribution. In short, these data offer the most accurate characterization available to date of the distribution of daily soil ingestion rates for children, and this PDF is recommended for use in the stochastic analysis of exposure via soil ingestion for children in an urban residential setting.

The PDF for child soil ingestion rates utilized in this study is representative of average contact rates among studied children who do not display obvious pica behavior (intentional soil eating). As discussed further in the uncertainty analysis section, we consider pica behavior to be an exceptional activity with respect to occurrence (i.e., percentage of children who exhibit pica behavior in the general population of children), exposure frequency (i.e., number of days per month or per year that pica occurs), and exposure duration (i.e., relevant age range for pica activity). Based on the preceding review, in our view the upper bound estimates of daily soil ingestion in the Stanek et al. (2001) study in a conservative risk assessment would account for the vast majority of typical children as well as those with mild or infrequent pica behaviors during childhood.

Body Weight Brainard and Burmaster (1992) used body weight data for adults from the NHANES II survey to construct separate lognormal PDFs for men and women. A PDF was derived that combines the data for both men and women, assuming that the proportion of each gender in the population is 50% (Finley et al., 1994). The lognormal PDF of body weight for adults of both genders has an arithmetic mean of 71 kg and a standard deviation of 15.9 kg. The 50th and 95th percentiles are 70 kg and 101 kg, respectively.

Burmaster and Crouch (1997) derived gender- and age-specific PDFs for children's body weight from the results of NHANES II, expressed in 1-yr age increments (0.5–1 yr, 1–2 yr, etc.). The resulting PDF for children has a lognormal distribution, with an arithmetic mean of 14.9 kg and a standard deviation of 4.0 kg. The 5th, 50th, and 95th percentiles are 9.2, 14.4, and 21.8 kg, respectively.

TCDD Cancer Potency As discussed earlier in the Dose-Response section, various low-dose extrapolation methods have been developed as possible cancer potency indicators for TCDD based

primarily on the Kociba et al. (1978) rat cancer bioassay, but also including bioassays done by the U.S. National Toxicology Program (NTP, 1982, 2004). Various cancer potency distributions that in our view are consistent with the cancer potency estimates from various regulatory agency or other researchers (see Table 2) include:

1. Point estimates: 9600 (Keenan et al., 1991); 16,000 (Crouch et al., 2005); 75,000 (Goodman & Sauer, 1992); 156,000 (U.S. EPA, 1985); 250,000 (Aylward et al., 2005b); and 1,000,000 $(mg/kg/d)^{-1}$ (U.S. EPA, 2003).
2. Uniform distributions: 9600 to 156,000; 9600 to 250,000; and 9600 to 1,000,000 $(mg/kg/d)^{-1}$ based on the point estimates just listed.
3. Triangular distributions: 9600 to 156,000 with apex of 75,000; 9600 to 250,000 with apex of 75,000; and 9600 to 1,000,000 with apex of 75,000 $(mg/kg/d)^{-1}$ based on the point estimates just listed and professional judgment that the Goodman and Sauer (1992) 75,000 estimate represents a conservative yet well-supported upper bound estimate.
4. Lognormal distributions: 9600 to 156,0000 with mean of 42,300 (mean midrange between 9600 and 75,000 estimates); 9600 to 156,000 with mean of 75,000; 9600 to 250,000 with mean of 75,000; and 9600 to 1,000,000 with mean of 75,000 $(mg/kg/d)^{-1}$.

Representative CPF distributions described here are illustrated in Figure 2.

Each of these above distributions represents a different weighting scheme for predicted cancer potency based on data from TCDD animal cancer bioassays or limited occupational epidemiology studies. The cancer potency distributions are relatively conservative in that they are each truncated on the low end at 9600 $(mg/kg/d)^{-1}$ and also include the current U.S. EPA estimates of 156,000 and 1,000,000 $(mg/kg/d)^{-1}$. Except for the 16,000 value reported by Crouch et al. (2005) for the NTP (2004) study, all cancer potency assumptions from animal studies are based on low-dose extrapolations using the linearized multistage model applied to the Kociba et al. (1978) study female rat tumor response, a model that is generally thought to overestimate the true risk. Three triangular and four lognormal distributions for cancer potency were also evaluated. These are centered on the more accurate and reliable tumor incidence estimates from the Pathology Working Group (PWG, 1990a, 1990b) reevaluation of the Kociba et al. (1978) study pathology slides. Three of the lognormal distributions are centered around the Goodman and Sauer (1992) estimated potency of 75,000 $(mg/kg/d)^{-1}$, and one lognormal PDF is centered at a mid-point potency value, 42,300 $(mg/kg/d)^{-1}$, between 75,000 and the 9600 value proposed Keenan et al. (1991). Upper bound cancer potency estimates based on the two rodent cancer bioassays conducted by the National Toxicology Program (NTP, 1982, 2004) are at the low end of this range. These distributions represent a reasonably conservative, yet plausible, range of cancer potency estimates that are considered most reliable based on the current weight of scientific evidence in our view.

Although it is only a proposal and many questions have been raised about the scientific underpinnings, the U.S. EPA proposed CPF of 1,000,000 was incorporated into this analysis for illustration purposes. A possible "corrected" upper bound CPF based on epidemiological studies of dioxin workers was as high as 250,000 $(mg/kg/d)^{-1}$ based on Aylward et al. (2005b) was also included. As discussed earlier, however, we believe that the scientific evidence supporting these higher CPFs based on admittedly limited epidemiology dose-response information is tenuous at this time.

Adult Soil Ingestion Rates Developing a meaningful PDF for adult soil ingestion is difficult because this topic has not been investigated as thoroughly as for child soil ingestion rates. Limited studies bearing on adult soil ingestion rates have been published in conjunction with the Anaconda studies performed by Calabrese et al. (1987, 1990, 1997a, 1997b) and Stanek et al. (1997). Calabrese et al. (1987) estimated adult soil ingestion rates between 1 and 100 mg/d based on fractional estimates of earlier Centers for Disease Control estimates. Pilot studies by Calabrese et al. (1990) involving 6 adults intentionally ingesting measured amounts of soil (50 to 500 mg/day) were estimated to have ingested between 30 and 100 mg/d of additional soil. Ten adult volunteers ingested known quantities of soil and the authors calculated that the adult volunteers incidentally ingested on average between 20 and 40 mg/d of soil in addition to the amount intentionally ingested

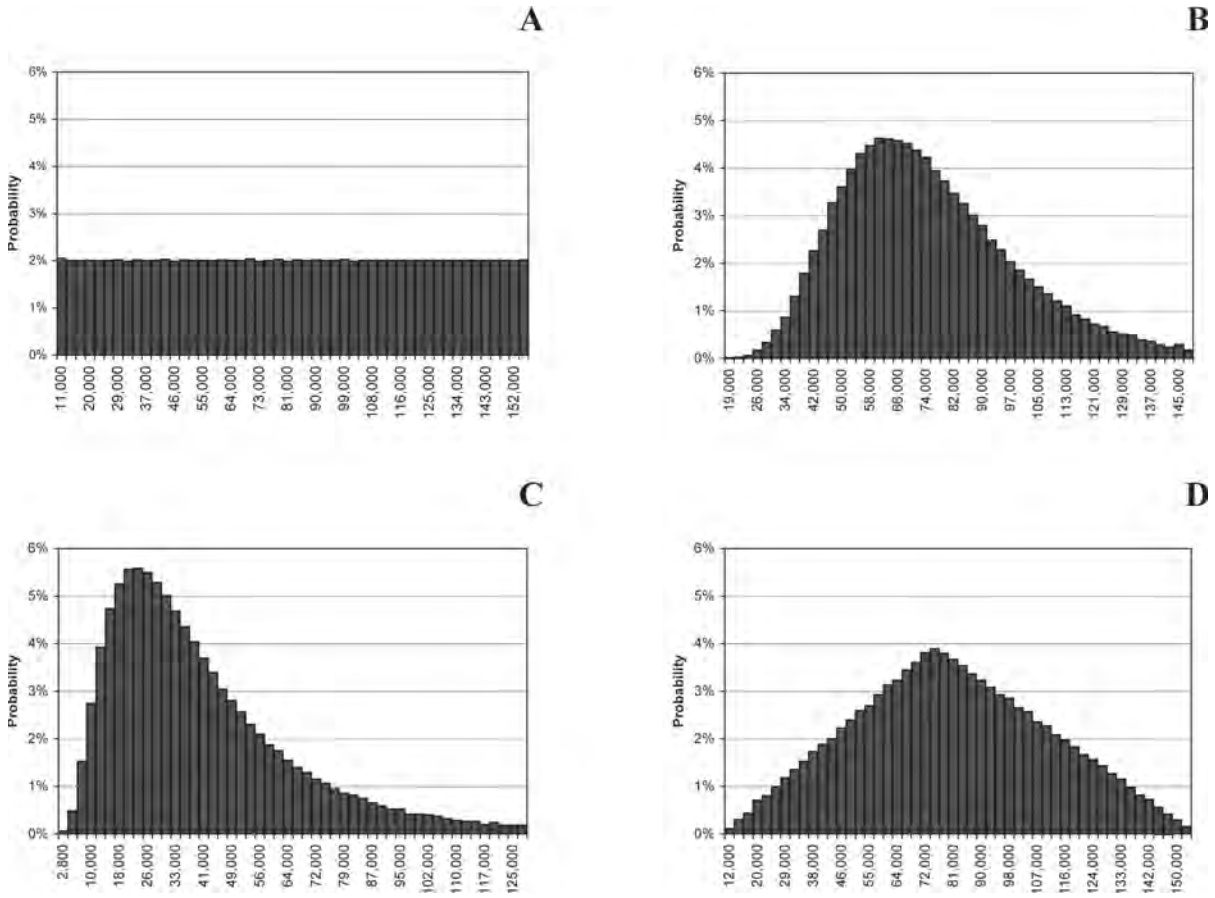

FIGURE 2. Probability density functions for four selected TCDD cancer potency distributions used for risk characterization: (A) Uniform distribution from 9600 to 156,000 per mg/kg/d. (B) Lognormal distribution with mean of 42,300 and range from 9600 to 156,000 per mg/kg/d. (C) Lognormal distribution with mean of 75,000, ranging from 9600 to 156,000 per mg/kg/d. (D) Triangular distribution from 9600 to 156,000 with midpoint of 75,000 per mg/kg/d.

(Calabrese et al., 1997a, 1997b). Another study reported an average value of 10 mg/d and a plausible upper bound range of 20 to 40 mg/d (Stanek et al., 1997), but the number of adults evaluated was small ($n = 6$). The Anaconda database for adult soil ingestion rates is small compared to that which exists for children (280 subject-days for adults versus 1100 subject-days for children).

The U.S. EPA default soil ingestion rate for adults in a residential scenario is 50 mg/d (U.S. EPA, 1997a). Gephart et al. (1994) evaluated the fecal tracer data of Calabrese et al. (1990) and concluded that an estimate of between 1 and 10 mg/d for adult soil ingestion (based on zirconium, considered the most reliable tracer) is likely to be a conservative estimate of soil ingestion rate in adults. A report by Krablin (1989) approximated adult soil intake at 10 mg/d based on analysis of mouthing behavior, activity patterns, and environmental arsenic intake and excretion among 26 subjects. Hawley (1985) evaluated data on adult activity patterns and fractional ingestion of soil load measured on the hands during gardening to approximate average soil ingestion at about 60 mg/d. Sheppard (1995) performed similar calculations and arrived at an estimate of 20 mg/d. However, the study designs for these reports do not sufficiently consider mass balance as did the Anaconda studies.

The PDF for adult soil ingestion was constructed primarily based on the results of adult subjects in the Anaconda studies, although the other published reports are reasonably represented as well. A lognormal distribution was assumed, with a range of 10 to 100 mg/d and a mean of 30 mg/d, which

represents the middle of the range (20 to 40 mg/d) identified by Calabrese et al. (1997a, 1997b) as the most plausible range for 10 adult subjects and by Stanek et al. (1997) as the upper bound range for 6 additional adults. This PDF should be updated if more definitive data become available, but in our view it represents a conservative set of assumptions that address uncertainties with regard to exposures from adult activities with heavier soil contact (e.g., gardening or construction).

Dermal Bioavailability Dermal bioavailability is a measure of the fraction of a chemical that can be released from the soil matrix and subsequently absorbed through the skin. Dermal bioavailability of TCDD in soils was evaluated by U.S. EPA (1992) in its dermal exposure assessment guidance based on four key studies (U.S. EPA, 1991; Roy et al., 1990; Poiger & Schlatter, 1980; Shu et al., 1988). Poiger and Schlatter (1980) reported data on dermal uptake of TCDD from different soil types and activated carbon in hairless rats, showing that uptake was very limited when TCDD was applied in activated carbon and that uptake was about sevenfold lower for a high organic carbon content soil (11.2% organic carbon) compared to a low organic carbon content soil (0.4% organic carbon). Shu et al. (1988) also reported data on in vivo dermal uptake from the clipped backs of haired rats using TCDD contaminated soils from Times Beach, Missouri. The U.S. EPA (1991) and Roy et al. (1990) performed absorption rate studies of TCDD in low and high organic carbon content soils in rats (in vivo and in vitro) and in human cadaver skin. Taking these studies into consideration, U.S. EPA (1992) derived a range for human skin percent TCDD absorbed from soils at 0.1 to 2.5%. They also suggested that the low end of the range be used for soils with high organic carbon content, and the high end for soils with low organic carbon content.

Banks and Birnbaum (1991) evaluated dermal uptake of neat TCDD applied to the clipped backs of haired rats and reported an absorption rate of 0.005/h when occluded over 5 d. Although this study didn't evaluate a soil matrix, an upper bound human-adjusted percent absorbed relevant to soils has been approximated at 1.75% (MDEQ, 2001). No in vivo human studies were found that identified an estimate for TCDD or other PCDD/F dermal bioavailability.

The PDF for dermal bioavailability is assumed to be a lognormal distribution with a range of 0.1 to 2.5% (U.S. EPA, 1992) and a mean value of 1%, which is intended to represent average uptake from soils with lower organic carbon content at the high end of the bioavailability range. This PDF is based primarily on animal data and in vitro human skin tests, but includes the full range of relevant published estimates of absorbed fraction from soils and in our view is conservative because the distribution is centered on a relative upper bound value.

Site-specific adjustment factors might be appropriate for high organic carbon content soils (e.g., >10% organic carbon), since this distribution will overstate probable dermal bioavailability in such cases, especially for upper percentile soil cleanup criteria. Also, dermal bioavailability is likely to decrease with higher molecular weight (>400) and greater polarity (U.S. EPA, 1992), and hence sites with TEQ dominated by the higher chlorinated congeners (e.g., hexa-, hepta-, and octaCDD/Fs) are also expected to exhibit lower dermal uptake than that indicated by this PDF.

Oral Bioavailability/Bioaccessibility Oral bioavailability is a measure of the fraction of a chemical that can be released from the soil matrix in the gastrointestinal tract and subsequently absorbed. The available studies in animals and humans suggest that oral bioavailability of TCDD is high (e.g., 80–90%) when administered in a lipophilic vehicle like corn oil or emulphor (Diliberto et al., 1996; Poiger & Schlatter, 1986; Rose et al., 1976) or when ingested with foods (Kociba et al., 1978). The oral bioavailability of TCDD decreases when it is associated with a soil matrix, and this effect becomes more pronounced over time (Poiger & Schlatter, 1980; Ruby et al., 2002). As postulated by Paustenbach et al. (1986), the U.S. EPA concluded that oral bioavailability of PCDD/Fs in soil will vary depending on factors such as soil type (composition and chemistry), time of contact between PCDD/Fs and soil (i.e., extent of aging), concentration of PCDD/Fs in soil, size of the PCDD/F dose, and the specific congeners present (U.S. EPA, 2003).

Several studies have assessed the oral bioavailability of TCDD in soils from contaminated sites with very high concentrations (e.g., sometimes >300 ppb TCDD in soil) (Bonaccorsi et al., 1984; Lucier et al., 1986; McConnell et al., 1984; Shu et al., 1988; Umbreit et al., 1986; van den Berg et al., 1985). Oral bioavailability in soils obtained from the Seveso, Italy, incident and from Times Beach, MO, ranged from about 25 to 50% (Bonaccorsi et al., 1984; Lucier et al., 1986; Shu et al.,

1988); these were in the 1–5 ppb range. Kimbrough et al. (1984) assumed 30% bioavailability in the Times Beach risk assessment based on data from McConnell et al. (1984) and Poiger and Schlatter (1980). Lucier et al. (1986) attributed 25 to 50% bioavailability to the McConnell et al. (1984) study, whereas Umbreit et al. (1986) reported that testing in 9 different soils ranged from 0.5 to 63%, averaging 35% (some of these soils were from the highly contaminated 80 Lister Avenue site in Newark, NJ, which contained TCDD up to 50,000 ppb, averaging about 660 ppb). The oral bioavailability of TCDD adsorbed to material with low organic content but high surface area (e.g., activated carbon), such as fly ash, appears to be significantly lower, perhaps 1–10% (van den Berg et al., 1985).

Ruby et al. (2002) presented the results of an *in vitro* PCDD/F bioaccessibility study of soils in the Midwestern United States area. In contrast to in vivo bioavailability determinations, their study was designed to determine in vitro bioaccessibility, that is, the fraction of PCDD/Fs that may be released from the soil matrix and be available for systemic absorption (Fehling et al., 2001; Ruby et al., 2002). The tested soils had low TCDD levels (<0.14 ppb) and TEQ levels (<0.34 ppb) compared to most soils examined in previous studies. The soils were sandy to sandy-loam types, showing relatively low organic carbon content, which is expected to increase oral bioavailability. Also, the PCDD/Fs were likely deposited more than 30 yr prior, and hence the soils were well aged/weathered over time (Ruby et al., 2002). The mean value for bioaccessibility was 25% across all PCDD/F congeners (range: 19–34%). Bioavailability can be conservatively assumed to be equal to bioaccessibility (which is assumed here), or it could be a fraction of this maximum amount that becomes solubilized.

The PDF for oral bioavailability was a lognormal distribution with a range of 0.5 to 63% and a mean value of 35%, which is intended to represent soils with lower organic carbon content at the high end of the bioavailability range. This PDF is based on limited data, but includes the full range of relevant published estimates of absorbed fraction and in our view is conservative because the distribution is centered on a value (35%) that is higher than most of reported estimates to date.

Site-specific adjustment factors might be appropriate for high organic carbon content soils (e.g., >10% organic carbon) since this distribution will overstate probably oral bioavailability in such cases, especially for upper percentile soil cleanup criteria. Also, oral bioavailability is known to decrease among highly chlorinated congeners like OCDD (Birnbaum & Couture, 1988; Norback et al., 1975), and hence sites with TEQ dominated by the higher chlorinated congeners (e.g., hepta and octaCDD/Fs) are expected to exhibit lower oral uptake than that indicated by this PDF.

Point-Estimate Values

Exposure Frequency The standard U.S. EPA default value for the number of days per year that a resident may be present at their house is 350, and this value was used as a point-estimate value for both the soil ingestion and dermal contact pathways for the child and adult scenarios (U.S. EPA, 1991). Site-specific considerations may support the use of alternative exposure frequency for resident exposures, which would change the calculated soil criteria in a linear manner.

Meteorological Factor A default meteorological factor for dermal contact is 1.0, indicating that potential exposures would be probable all year. Depending on the location of the site of interest, often it will be appropropriate to use an alternative meteorological factor for evaluating resident exposures, which would change the calculated soil criteria in a linear manner. For example, a meteorological factor of 0.67 has been employed in Midwestern U.S. cities where adverse weather conditions (e.g., rain, muddy soil, frozen soil, soil covered with snow) precludes soil contact for about one-third of the year or more. Studies have found that soil ingestion rates decrease significantly during times of precipitation (van Wijnen et al., 1990). The available information, on average, suggests that only about one-third of indoor dust is derived from outdoor soil (Paustenbach et al., 1997; Calabrese & Stanek, 1992).

Averaging Time The U.S. EPA default averaging time for carcinogen assessment is 25,550 d (a 70-yr lifespan), and this value was used as a point estimate in this assessment (U.S. EPA, 1991).

Body-Part-Specific Skin Surface Area The percentage of total body surface area that each exposed part represents was considered in the stochastic analysis as a point estimate. For both children and adults, it was assumed that an individual might potentially be exposed on hands, forearms, lower legs, feet, and face.

For children, the percentage of total skin surface area represented by each body part was obtained from the U.S. EPA *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2000a) and is the arithmetic average of boys and girls for age 6 or younger (Table 11). These fractions were multiplied by the total surface area PDF and correlated with body-part-specific soil-to-skin adherence values in the stochastic analysis.

For adults, the percentage of total skin surface area represented by the hands, forearms, and face was obtained from U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997a) as shown in Table 12. These fractions were used in the same manner as the child skin surface areas in the stochastic analysis.

Target Cancer Risk Level A target risk level of 1×10^{-5} was used in the calculation of the soil criterion. This target level is within the range identified by U.S. EPA as being acceptable for cleanup of hazardous waste sites (10^{-4} to 10^{-7}) (U.S. EPA, 1989b). It is the same target risk level (10^{-5}) for carcinogenic effects identified in the U.S. EPA guidance for risk assessment of incinerators (U.S. EPA, 1998) and used under California's Proposition 65 and other right-to-know legislation (OEHHA, 2004). Lastly, Travis et al. (1987) reported that the vast majority of decisions regarding sites where contaminants are a concern have not been sufficient to warrant significant attention at risks below this level. Although the Travis et al. (1987) analysis has not been updated in several years, in our experience these conclusions still apply today.

Calculation of Urban Residential Soil Criteria Based on Noncancer Hazard Index

The PCDD/Fs soil criterion was calculated for a noncancer hazard index of 1.0, consistent with U.S. EPA risk assessment guidance (U.S. EPA, 1989b). With the following exceptions, the methodology utilized to derive soil clean-up criteria based on noncancer risk was identical to that described for cancer risk.

An average daily dose (ADD) was calculated in lieu of the lifetime average daily dose (LADD). The ADD is higher and more conservative than the LADD because the exposure duration and averaging time are set equal to each other. If one assumes an average residential tenure of 9 yr, the calculated ADD would be nearly 12-fold higher than the LADD; an assumed residential tenure of 30 yr would result in an ADD 3.5-fold higher than the LADD.

Although there is no current reference dose for PCDD/Fs that is endorsed by U.S. EPA (U.S. EPA, 2003), we have used comparable safe dose benchmarks developed by other public health agencies (e.g., ATSDR and WHO) and based on an assumed RfD of 5 pg/kg/d as proposed by Greene et al. (2003). This analysis includes point estimate noncancer toxicity criteria ranging from 1 to 20 pg/kg/d proposed by other agencies (ATSDR, 1998; European Commission, 2001; WHO, 2000, 2001). The influence of applying weighted distributions of these RfD-equivalent criteria was also examined, as is most relevant to the exposure type and duration under study. As explained further here and in the Sensitivity Analysis section, the parameters that most prominently influence the dose, risk, and uncertainty in the risk characterization are those assumed for child soil ingestion rate and duration of residence.

It may be reasonable to assume that doses calculated based on upper bound soil ingestion rates for children are best compared to a reference dose for subchronic exposure. This takes into account the limited duration of higher soil ingestion periods relative to the human lifespan (e.g., peak exposures during selected days and seasons at ages 0 to 6 yr). Only ATSDR (1998) has proposed a subchronic or "intermediate" MRL value (20 pg/kg/d) that may serve as an appropriate point estimate benchmark dose for PCDD/F soil ingestion exposures to children. Conversely, the ATSDR (1998) chronic MRL (1 pg/kg/d), based on assumed daily exposure for an entire lifetime, is most relevant to chronic exposures (e.g., 30 yr to an entire human lifespan). As such, it seems reasonable to include this range (1–20 pg/kg/d) of reference doses in the form of probability distributions that are

weighted to favor estimates (e.g., 20 pg/kg/d for intermittent high soil ingestion in children) that provide a better match between the dose estimate and the toxicity criterion with respect to exposure frequency and duration for the risk-driving components.

In our risk characterization for an urban residential setting, two sets of ADD distributions with corresponding soil dioxin TEQ cleanup criteria were calculated: (1) a "child-only" ADD based on a truncated distribution of residential exposure duration (at 6 yr) that assumes only child exposures, and (2) a "child-adult" ADD that includes the full distribution of residential exposure duration (1 to 30 yr) but always includes the first 6 yr as childhood exposure. This allowed us to separately examine the implications of different assumptions about the applicable reference dose distribution for longer-term residents without ignoring potentially higher childhood exposures (e.g., intake).

To conduct a more thorough evaluation of the implications of differing conclusions about appropriate toxicity criteria for noncancer effects of TCDD, the following reference dose assumptions were considered:

1. Point estimates: 1 pg/kg/d (ATSDR, 1998, chronic MRL); 2 pg/kg/d (CoT, 2001, TDI); 4 pg/kg/day (WHO, 2000, upper bound TDI); 5 pg/kg/d (Greene et al., 2003, proposed RfD); and 10 pg/kg/d (Japan, 1996, as cited in Larsen et al., 2000).
2. Uniform distributions: 0.5 to 5 pg/kg/d based on plausible current PCDD/F dietary TEQ to 10-fold higher; 1 to 4 pg/kg/d (WHO, 2000, TDI range); 1 to 10 pg/kg/d (up to Japan, 1996, ADI); and 1 to 20 pg/kg/d (up to ATSDR, 1998, intermediate MRL).
3. Lognormal distributions: 0.5 to 5 with mean of 1.5 pg/kg/d; 1 to 4 with mean of 2 pg/kg/d; 1 to 10 with mean of 3.3 pg/kg/d; 1 to 20 with mean of 8.7 pg/kg/d (preceding means chosen as about one-third of maximum value); and 1 to 20 with mean of 13 pg/kg/d (mean chosen as two-thirds of maximum value).

Representative distributions described above are illustrated in Figure 3.

As noted earlier; longer term residential exposures as calculated in our child-adult ADD distributions may be more applicable to lower reference dose assumptions, such as 1–10 pg/kg/d, due to the fact that such "chronic" exposure durations (measurable in decades) may comprise a substantial fraction of the human lifespan. Conversely, reference dose distributions weighted more toward the 20 pg/kg/d "intermediate" duration MRL may be more appropriate for the child-only ADD comparisons, especially at the upper percentile dose estimates, which are dominated by likely intermittent, age-specific peak exposure activities during early childhood. In our view, these distributions represent a conservative yet plausible range of reference dose assumptions that are considered most applicable to our calculations of child-only and child–adult ADDs, based on the weight of scientific evidence to date. Specifically, recent studies have confirmed that the half-lives of PCDD/Fs in young children are 3 to 7 mo (Kreuzer et al., 1997; Leung et al., 2005a). Adult half-lives of the assumed most potent congeners (TCDD and PeCDD/F) range from 7 to 15 yr (Geyer et al., 2002; Flesch-Janys et al., 1996). The shorter half-lives of these congeners in young children equate with lower tissue concentrations and lower health risks compared to adults exposed at the same daily dose rate. Use of an age-dependent toxicokinetic model for estimating childhood body burdens of PCDD/Fs reveals the limited impact of dietary (including breastfeeding) and environmental (e.g., soil ingestion) sources of exposure (Kerger et al., 2005b; Paustenbach et al., 2004). These findings are directly applicable to the current study in that the vast majority of dose for both the cancer and noncancer risk assessments are derived from assumed soil ingestion exposures in young children.

RISK CHARACTERIZATION

Risk characterization is the process of estimating the incidence of a health effect under various exposure conditions by combining the exposure and dose-response assessments and describing the underlying uncertainties of those estimates (NAS, 1983; Williams & Paustenbach, 2002). In the following subsections, we present risk-specific dioxin TEQ dose and cleanup level distributions based on

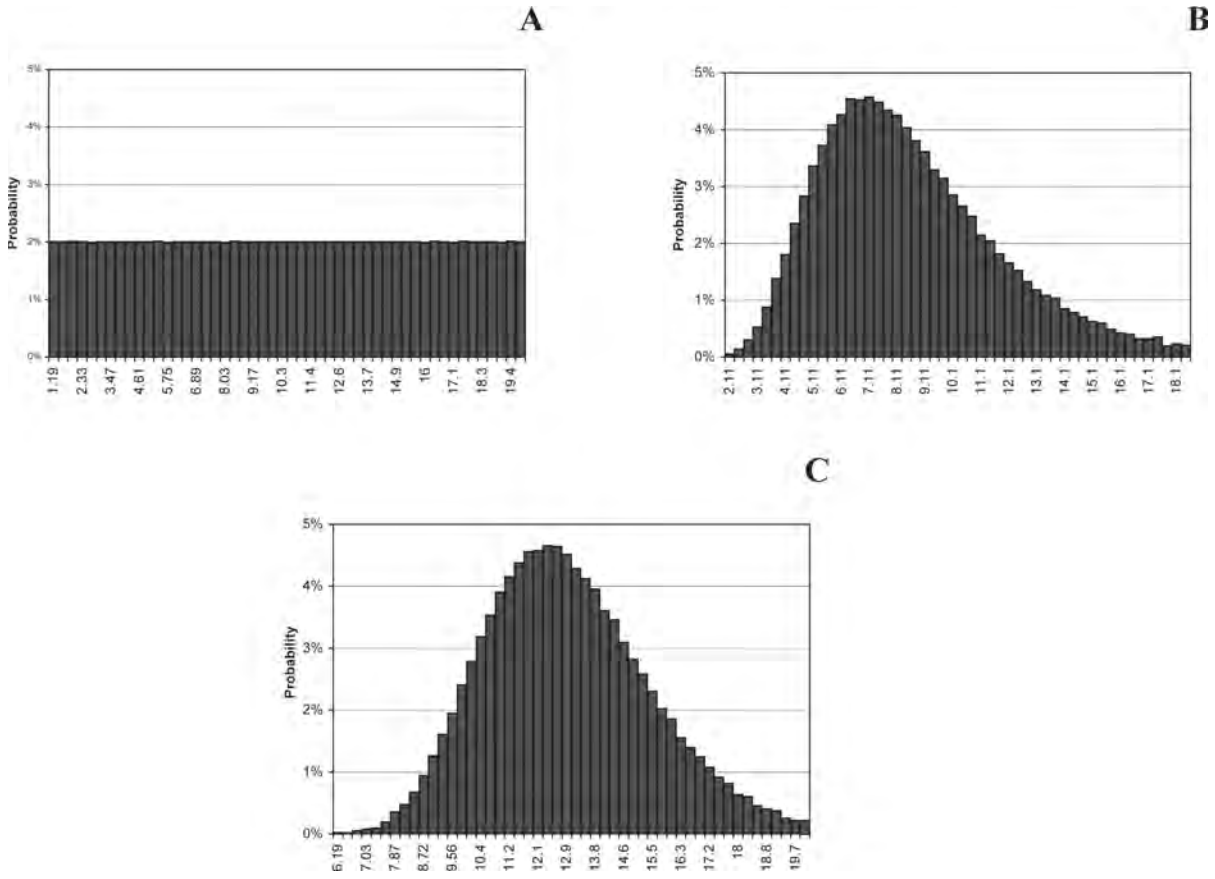

FIGURE 3. Probability density functions for three selected TCDD noncancer risk criteria distributions used for risk characterization. (A) Uniform distribution from 1 to 20 pg/kg/d. (B) Lognormal distribution with mean of 8.67 and standard deviation of 4.0 pg/kg/d. (C) Lognormal distribution with mean of 13.2 and standard deviation of 4.0 pg/kg/d.

probabilistic risk assessment methods described in earlier sections. These probabilistic calculations adopt a fixed target level for cancer risk of 1 per 100,000 and a noncancer hazard index of 1.0. They were evaluated separately.

Distribution of Health-Based Soil Criteria for an Urban Residential Setting Based on Cancer Risk

The results of the stochastic analysis of soil cleanup levels using several different cancer potency assumptions for an urban residential setting are presented in Table 13.

The 1st, 5th, 10th, and 50th percentiles of the dioxin TEQ soil cleanup criteria distribution (the lowest to the mean soil TCDD-equivalent concentrations) are represented in Table 13 as being protective of the potentially exposed population at the 99th, 95th, 90th, and 50th percentiles, respectively. The 50th percentile values represent the central tendency or most likely average distribution of dioxin TEQ doses and soil cleanup levels, while the 90th to 99th percentile values represent the range of conservative upper bound estimates that are sometimes considered in risk management decisions.

The selected urban residential soil criteria for PCDD/Fs in Table 13 show a range of values based on the results of the stochastic analysis, spanning nearly 3 orders of magnitude from the most conservative value (0.03 ppb at the 99th percentile, CPF point estimate of 1,000,000 $(mg/kg/d)^{-1}$) to the least conservative value of 22 ppb at the 50th percentile, CPF point estimate of 9,600 $(mg/kg/d)^{-1}$.

TABLE 13. TCDD-Equivalent (TEQ) Soil Cleanup Level and Lifetime Average Daily Dose (LADD) at 50th to 99th Percentile Protection Levels for Selected Cancer Potency Assumptions at an Incremental Cancer Risk of 1 per 100,000 and No Site-Specific Adjustments

Cancer potency assumption	50th Percentile soil cleanup level in ppb [LADD in pg/kg/d]	90th Percentile soil cleanup level in ppb [LADD in pg/kg/d]	95th Percentile soil cleanup level in ppb [LADD in pg/kg/d]	99th Percentile soil cleanup level in ppb [LADD in pg/kg/d]
Point estimates:				
9600 per mg/kg/d	22 [0.11]	7.1 [0.39]	5.5 [0.52]	3.4 [0.94]
16,000 per mg/kg/d	13 [0.068]	4.2 [0.24]	3.3 [0.32]	2.1 [0.58]
75,000 per mg/kg/d	2.7 [0.013]	0.91 [0.046]	0.70 [0.062]	0.44 [0.11]
156,000 per mg/kg/d	1.3 [0.0068]	0.44 [0.024]	0.38 [0.032]	0.21 [0.058]
250,000 per mg/kg/d	0.82 [0.0042]	0.27 [0.015]	0.21 [0.020]	0.13 [0.036]
1,000,000 per mg/kg/d	0.21 [0.00097]	0.07 [0.0034]	0.05 [0.0046]	0.03 [0.0083]
Uniform distributions:				
9600 to 156,000 per mg/kg/d	3.1 [0.010]	0.75 [0.037]	0.54 [0.049]	0.32 [0.089]
9600 to 250,000 per mg/kg/d	2.0 [0.0064]	0.48 [0.023]	0.35 [0.031]	0.20 [0.055]
9600 to 1,000,000 per mg/kg/d	0.52 [0.0016]	0.12 [0.0057]	0.09 [0.0077]	0.05 [0.014]
Triangular distributions:				
9600 to 156,000 per mg/kg/d, apex = 75,0000	2.8 [0.011]	0.82 [0.040]	0.60 [0.054]	0.35 [0.097]
9600 to 250,000 per mg/kg/d, apex = 75,000	2.1 [0.0077]	0.59 [0.028]	0.43 [0.037]	0.24 [0.066]
9600 to 1,000,000 per mg/kg/d, apex = 75,000	0.76 [0.0023]	0.17 [0.008]	0.12 [0.011]	0.07 [0.019]
Lognormal distributions:				
9600 to 156,000 per mg/kg/d, mean of 42,300	6.3 [0.017]	1.5 [0.061]	1.1 [0.082]	0.53 [0.15]
9600 to 156,000 per mg/kg/d, mean of 75,000	3.0 [0.012]	0.88 [0.044]	0.66 [0.059]	0.38 [0.11]
9600 to 250,000 per mg/kg/d, mean of 75,000	3.4 [0.0010]	0.85 [0.037]	0.60 [0.049]	0.32 [0.089]
9600 to 1,000,000 per mg/kg/d, mean of 75,000	9.8 [0.0042]	0.86 [0.015]	0.43 [0.02]	0.13 [0.036]

The span of cleanup levels at the 95th percentile under these cancer potency assumptions is from 0.05 to 5.5 ppb, and at the 99th percentile is 0.03 to 3.4 ppb. Note also that the lifetime average daily dose (LADD) estimates corresponding to the selected soil cleanup criteria in Table 13 are well below the tolerable intake levels for chronic exposure that the European Commission (2001) and WHO (2000, 2001) consider to be protective against both cancer and noncancer effects of TCDD and related compounds (Table 7).

U.S. EPA probabilistic risk assessment guidance recommends that the 90th to 99.9th percentiles of the risk distribution be used to assure adequately conservative decision making for risk management purposes (U.S. EPA, 2001b). When determining the percentile upon which the final soil criterion should be based, several factors should be considered. Primary among these are the review and evaluation of the potential limitations in the quality and relevance of the data that are used in the risk assessment (i.e., qualitative and quantitative uncertainties) in order to evaluate the strengths and weaknesses of the assessment. U.S. EPA guidance states:

> In human health [probabilistic risk assessment], a recommended starting point for risk management decisions regarding the [reasonable maximum exposure] is the 95th percentile of the risk distribution. (U.S. EPA, 2001b, p.)

Consistent with U.S. EPA guidance for protecting individuals at the upper bound of the risk range (the 95th percentile of risk in a forward calculation), the 95th percentile soil criteria shown in Table 13 can be considered reasonably conservative health-based values for an urban residential setting (U.S. EPA, 2001b). Notably, there is only a 40 to 50% difference between the 95th percentile soil

cleanup and dose estimates and those corresponding to the 90th or 99th percentile. In contrast, the 50th percentile or central tendency estimates of dose and cleanup levels differ from the 95th percentile values by about four- to fivefold (Table 13). The cleanup levels corresponding to the 95th percentile assuming CPFs in the range of 9600 to 156,000 per mg/kg/d vary between 0.4 to 5.5 ppb without any site-specific adjustment factors. Excluding the two lowest point estimate CPFs (9600 and 16,000) and those involving the CPFs based on a tenuous exposure/epidemiological analysis (250,000 and 1,000,000), all of the cleanup levels at the 95th percentile identified in Table 13 fall into the range of 0.4 to 1.1 ppb. In our view, these TEQ cleanup levels are adequately conservative to assure public safety in most urban residential settings. These values, with or without appropriate site-specific adjustment factors discussed later, are consistent with the 1 ppb action level for TCDD in soils identified two decades ago by the CDC (Kimbrough et al., 1984) and still considered to be protective of human health by ATSDR researchers (ATSDR, 1998; DeRosa et al., 1999a, 1999b; Pohl et al., 2002). It is worth noting that in 2005, ATSDR was giving serious thought to dropping the 1.0 ppb "action level" for dioxin in soil (ATSDR, 2005).

Use of the proposed epidemiology-based CPFs in the range of 250,000 to 1,000,000 per mg/kg/d drops the 95th percentile cleanup level to 0.05 to 0.2 ppb if point estimates are employed, and 0.09 to 0.6 ppb if these higher values are included in the selected broader range of possible CPFs, for example, 9600 to 1,000,000 per mg/kg/d. However, we believe these higher CPF values based on admittedly limited epidemiology data for PCDD/Fs (IARC, 1997) are based on questionable exposure and response data. These higher values are inconsistent with the most sensitive species/tumor findings from three rodent cancer bioassays (Kociba et al., 1978; NTP, 1982, 2004). After proper pharmacokinetic adjustment and further validation of the epidemiology-based dose-response for cancer, it appears to us that there will be agreement that the range of CPF values that will be used in the coming years will like be between 50,000 to 150,000. It is also quite possible that PCDD/Fs will be broadly thought to act by a threshold-dependent mechanism (WHO, 2000, 2001; EC, 2001; CoT, 2001; Popp et al., 2005) and that no attributable cancer risk is likely at low doses (especially at the LADD doses examined in Table 13, all below 1 pg/kg/d).

The allocation of risk according to pathway (dermal vs. ingestion) and receptor (child vs. adult) under each of the assumed cancer potency distributions shows a common shift as illustrated in Figure 4. At the 50th percentile or central tendency estimate, soil ingestion and dermal contact doses during childhood comprise the vast majority of the estimated LADD (about 89%, Figure 4a). For example, at the 99th percentile, childhood soil ingestion and dermal contact together contribute about 69% of the total LADD (Figure 4b). This trend results from the conservative LADD calculation methods utilized. In large part, this pattern derives from a forced assumption in the LADD calculations that the first 6 yr of any resident's exposure occurs as a child. For example, LADDs calculated for residential exposure durations up to the average value of 9 yr are entirely or largely comprised of assumptions about childhood exposures, averaged over a lifetime. These LADDs fall near the middle of the LADD distribution, which includes exposure durations from 1 to 70 yr. At the higher percentiles (e.g., 99th), which incorporate the longest exposure durations (e.g., decades), the adult dermal and soil ingestion doses comprise a more substantial part of the LADD (about 31% each), while child soil ingestion still contributes about 69% due to high-end soil ingestion estimates (up to 137 mg/d).

Distribution of Health-Based Soil Criteria for an Urban Residential Setting Based on Noncarcinogenic Health Effects

The results of the stochastic analysis of soil cleanup levels based on several different noncancer toxicity criteria (i.e., assumed equivalent to the reference dose or RfD) for an urban residential setting are presented in Table 14 for the adult–child integrated ADD. The adult–child integrated ADDs were slightly higher than the child-only ADDs (data not shown). Again, the 1st, 5th, 10th, and 50th percentiles of the soil criteria distribution (the lowest to the mean soil TCDD concentrations) are represented as being protective of the potentially exposed population at the 99th, 95th, 90th, and 50th percentiles, respectively. The rows have been listed in order from smallest to largest cleanup level (and corresponding ADD dose) at the 95th and 99th percentiles.

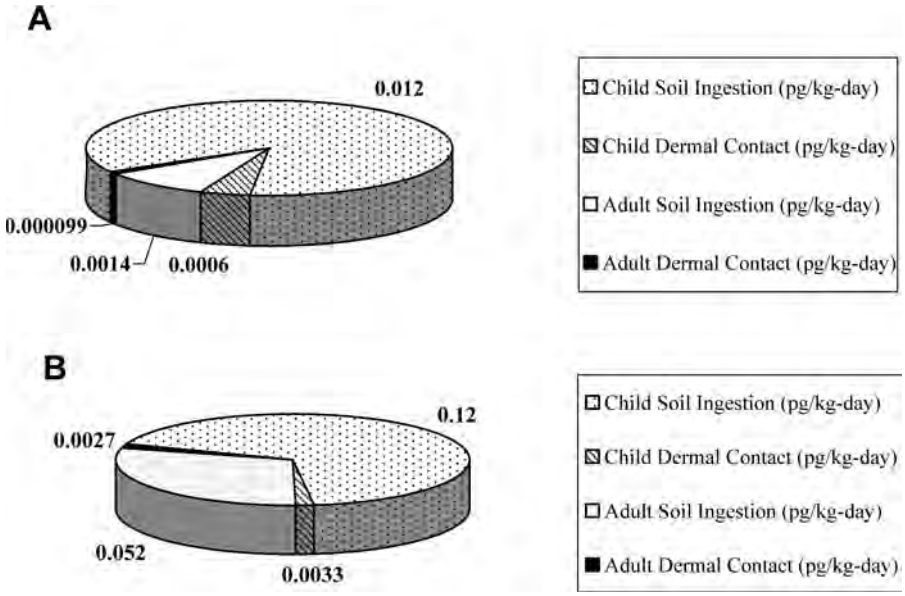

FIGURE 4. Charts describing 50th percentile and 99th percentile contribution to lifetime average daily dose by exposure pathway for the adult and child (age 0–6 yr) scenarios. [a] Based on soil criterion calculated using a lognormal distribution with a mean of 42,300 per mg/kg/day for CPF.

The selected urban residential soil cleanup criteria for PCDD/Fs for the child–adult ADDs in Table 14 show a range of values based on the results of the stochastic analysis, all of which are comparable to or greater than the clean-up levels at the same percentile in Table 13 based on a 1 in 100,000 incremental lifetime cancer risk. The selected soil cleanup values in Table 14 span more than an order of magnitude from the most conservative value (0.3 ppb at the 99th percentile, RfD of 1 pg/kg/d) to the least conservative value (19 ppb at the 50th percentile, lognormal RfD distribution ranging from 1 to 20 pg/kg/d, with mean of 13.2). The span of cleanup levels at the 95th percentile under these reference dose assumptions is from about 0.5 to 5.7 ppb, and at the 99th percentile is 0.3 to 3.6 ppb without any adjustment for site-specific factors. The cleanup criteria at the 95th percentile that are centered around a proposed RfD range of 2 to 5 pg/kg/d fall in the range of about 0.8 to 2.3 ppb, whether represented as point estimates, uniform distributions, or lognormal distributions. This range of cleanup values is adequately conservative to assure public health protection in our view, and is consistent with the former CDC action level of 1 ppb for residential settings.

The central tendency and upper percentile ADD estimates in Table 14 are largely driven by the child soil ingestion parameters included in each set of calculations. Figure 5 provides an illustration of the proportional contribution of each pathway on the child–adult ADDs at the 50th and 99th percentiles assuming a lognormal RfD distribution (1–20 pg/kg/day with mean of 13.2). At the 50th percentile, child soil ingestion comprises about 78% of the estimated ADD, and total childhood exposures (dermal and ingestion) contribute about 82% (Figure 5a). Child soil ingestion is even more dominant at the 99th percentile, comprising 84% of the ADD, and total childhood exposures contribute about 86% (Figure 5b), As noted earlier pertaining to the LADD calculations, this dominance of the child soil ingestion pathway in the child–adult ADD estimates is driven in large part by consideration of the first 6 yr of any residential exposure as exposure to a young child, 0–6 yr old.

It is important to consider the qualitative and quantitative uncertainties involved in the cleanup criteria estimates illustrated in Table 14. The ADD dose is driven largely by child soil ingestion and exposure duration assumptions, and several toxicological considerations are expected to limit the true impact on noncancer risk. In particular, the shorter PCDD/F half-life in young children

TABLE 14. TCDD-Equivalent (TEQ) Soil Cleanup Level and Average Daily Dose (ADD) at 50th to 99th Percentile Protection Levels for Selected Noncancer Toxicity Criteria at Hazard Index = 1.0 and No Site-Specific Adjustments

Noncancer toxicity criteria (reference dose equivalent)	50th Percentile soil cleanup level in ppb [ADD in pg/kg/d]	90th Percentile soil cleanup level in ppb [ADD in pg/kg/d]	95th Percentile soil cleanup level in ppb [ADD in pg/kg/d]	99th Percentile soil cleanup level in ppb [ADD in pg/kg/d]
Point estimates:				
1 pg/kg/d	1.4 [0.15]	0.60 [0.43]	0.46 [0.57]	0.30 [0.96]
2 pg/kg/d	2.9 [0.28]	1.2 [0.84]	0.92 [1.1]	0.59 [1.9]
4 pg/kg/d	5.8 [0.58]	2.4 [1.7]	1.8 [2.3]	1.2 [3.8]
5 pg/kg/d	7.2 [0.72]	3.0 [2.1]	2.3 [2.8]	1.5 [4.8]
10 pg/kg/d	14 [1.5]	6.0 [4.3]	4.6 [5.7]	3.0 [9.6]
Uniform distribution:				
0.5 to 5 pg/kg/d	3.6 [0.18]	1.0 [0.52]	0.72 [0.7]	0.37 [1.2]
1 to 4 pg/kg/d	3.4 [0.25]	1.2 [0.74]	0.92 [0.99]	0.52 [1.7]
1 to 10 pg/kg/d	7.1 [0.37]	2.1 [1.1]	1.5 [1.4]	0.76 [2.4]
1 to 20 pg/kg/d	14 [0.48]	3.2 [1.4]	2.1 [1.9]	1.0 [3.2]
Lognormal distributions:				
0.5 to 5 pg/kg/d, mean 1.5	2.1 [0.15]	0.69 [0.43]	0.51 [0.57]	0.30 [0.96]
1 to 4 pg/kg/d, mean 2	2.8 [0.25]	1.1 [0.74]	0.83 [0.99]	0.52 [1.7]
1 to 10 pg/kg/d, mean 3.3	4.7 [0.33]	1.6 [0.96]	1.2 [1.3]	0.68 [2.2]
1 to 20 pg/kg/d, mean 8.7	12 [0.92]	4.3 [2.7]	3.2 [3.6]	1.9 [6.1]
1 to 20 pg/kg/d, mean 13	19 [1.7]	7.4 [5.1]	5.7 [6.8]	3.6 [12]

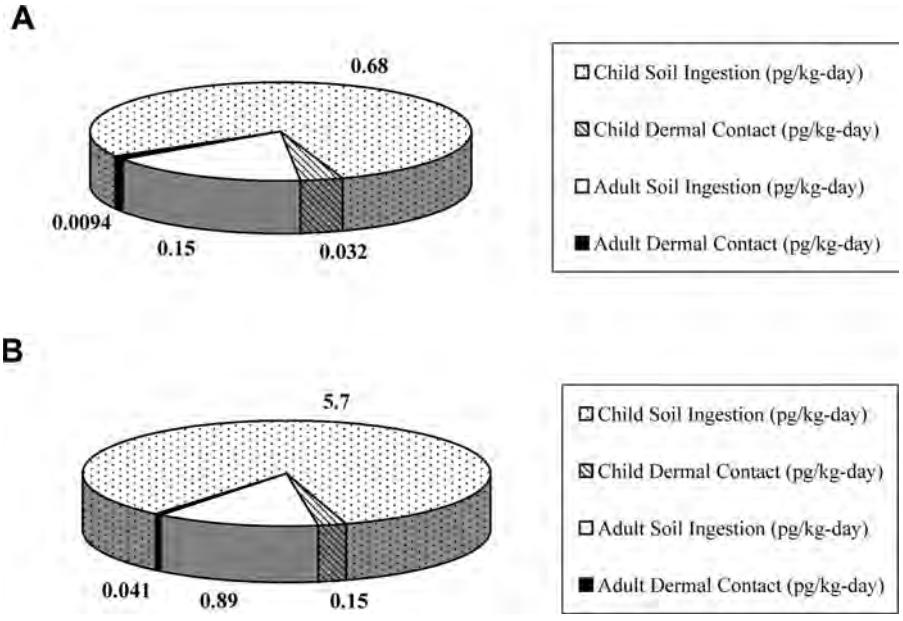

FIGURE 5. Charts Describing 50th percentile and 99th percentile contribution to average daily dose by exposure pathway for the adult and child (age 0–6 yr) scenarios. [a] Based on soil criterion calculated using a lognormal distribution with a mean of 8.67 pg/kg/day for the RfD.

(Leung et al., 2005a; Kerger et al., 2005a, 2005b) is expected to lead to lower tissue concentrations and health risks compared to adults exposed at the same dose rate. The potential limitations in the quality and relevance of the data and assumptions used in the risk assessment must be carefully weighed by the risk managers.

Site-Specific Adjustment of the Soil Cleanup Criteria

The soil cleanup criteria identified in Tables 13 and 14 have been weighted in several respects to represent reasonable maximum exposure conditions for several site-specific conditions. Key examples include the choice of upper bound values as the mean of PDFs for soil ingestion rates, for oral and dermal bioavailability, and for factors that might substantially alter exposure frequency (e.g., meteorological factor and substantial ground cover). Thus, the criteria in Tables 13 and 14 represent exposures that are least favorable (and most conservative or public health protective), given what is known in the literature about how site-specific conditions can influence exposure, absorption, and health risks.

For example, it is clear from the available studies on dermal and oral bioavailability that TCDD in soils with high organic carbon content (e.g., >10%) is poorly absorbed in mammals compared to that observed for lower organic carbon content (e.g., 0.4%). For dermal bioavailability, there is approximately a sevenfold difference between high and low organic carbon content soils (U.S. EPA, 1991; Roy et al., 1990; U.S. EPA, 1992). Similarly, Umbreit et al. (1986) and Van den Berg et al. (1983, 1985, 1987c) reported up to 2 orders of magnitude lower oral bioavailability in soil types with high organic carbon content and with fly ash (0.5–10%). If site-specific investigations demonstrate the influence of these factors, particularly with respect to oral bioavailability (since the child soil ingestion dose is key), a site-specific bioavailability adjustment factor may be considered appropriate in our view. Such a correction factor might be quantified as the ratio between the central tendency soil bioavailability assumed here (35%) and the average value justified by the soil organic carbon conditions.

A second reasonable site-specific adjustment factor might be justified based on exposure frequency, reflecting, for instance, limited access to the contaminated soils due to groundcover, weather conditions, rough terrain, or other factors. An example of such a factor would be a meteorological factor in the Midwestern United States where snow and frozen ground can largely preclude regular soil contact for perhaps one-third of each year. In such cases, a correction factor of 0.67 might be justified to adjust the soil cleanup criteria to site-specific conditions. Similarly, a correction factor for nonuniform distribution of PCDD/F contaminated soils may be appropriate in situations where construction, landscaping, and/or gardening activities require the use of imported soil, thus reducing resident contact frequency with historically contaminated soils.

A third reasonable site-specific adjustment factor might be justified in instances where the vast majority of soil TEQ is attributable to higher chlorinated congeners, particularly the hepta- and octa-CDD/Fs. Similar to the case for high organic carbon content, these higher chlorinated congeners demonstrate lower oral bioavailability (Birnbaum & Couture, 1988; Norback et al., 1975), possibly accounting for a factor of more than fivefold for OCDD. If site-specific investigations demonstrate the influence of these factors, particularly with respect to oral bioavailability (since the child soil ingestion dose is key), a site-specific bioavailability adjustment factor may be considered appropriate in our view. Such a correction factor might be quantified as the ratio between the central tendency soil bioavailability assumed here (35%) and the average value justified by bioavailability studies of the site-specific congener mixture.

Sensitivity Analysis

In this assessment, the exposure parameters used to derive the soil criteria are represented as either point-estimate values or PDFs and used to represent the variability and uncertainty of the exposure parameter. A sensitivity analysis was conducted to assess the influence of these parameters on soil criteria distributions. To simplify this discussion, the focus is placed on the soil criterion of 0.7 ppb, which is based on the 95th percentile protection level for cancer risk (1 in 100,000 incremental lifetime cancer risk), assuming a TCDD cancer potency value of 75,000 $(mg/kg/d)^{-1}$.

A sensitivity analysis presents the magnitude of the impact of each individual parameter on the derived soil criterion and evaluates the dependence of the soil criterion on each of the individual parameters. These analyses can assist in identifying and ranking the assumptions that are the most important sources of variability and uncertainty (i.e., which parameters, if changed, will have the greatest impact on the soil criterion).

Sensitivity of Soil Criteria to Age Groups Examination of the distribution of estimated daily doses for cancer risks (LADD, Figure 4) and for noncancer hazard (ADD, Figure 5) indicates that the dose received during childhood is approximately four- to eightfold higher than that received during adulthood based on 50th percentile values, and two- to sixfold higher based on 95th percentile values. On average, 82 to 89% of the daily dose is received during childhood exposure, with the remaining 11 to 18% received during adulthood. Therefore, the exposure parameters used to quantify childhood exposures have a greater effect on the soil criteria than those for adults.

Sensitivity of Soil Criteria to Exposure Pathways Two pathways of exposure were quantified in this assessment: incidental soil ingestion and dermal contact (see Figures 4 and 5). The distribution of estimated daily doses indicates that, typically, during childhood, the contribution from the ingestion pathway is about 95 to 97% of the child ADD. During adulthood, the typical contributions to the ADD are 94 to 96% for soil ingestion. Therefore, it can be concluded that the soil ingestion has a dominant influence the soil criterion.

Sensitivity of Soil Criteria to Exposure Parameters A visual evaluation of the exposure parameters for incidental soil ingestion and dermal contact, as shown as Eqs. (9) and (10), indicates that both are multiplicative equations, or "product-quotient models," as described in U.S. EPA probabilistic guidance (U.S. EPA, 2001b). Unlike other modeling equations that may involve squaring of variables or other mathematical operations, no variable in a product-quotient model affects the model output more significantly than another variable. The soil criterion follows a linear relation and is not significantly sensitive to any of the model variables due to mathematical operations.

The sensitivity of the soil criteria to each of the PDFs used was evaluated by analyzing the degree of variation in the model output (e.g., the soil criterion). Consistent with U.S. EPA guidance (U.S. EPA, 2001b), the Spearman rank correlation analysis was used to compare the soil criterion output distribution against the model input distributions (e.g., the PDFs) and provide a quantitative estimate of the sensitivity to each.

Figures 6 and 7 present the results of the Spearman rank correlation analysis. Figure 6 graphically displays the sensitivity of the soil criteria to specific PDFs. In general, a correlation coefficient (R) can range from −1 to 1. An R of 0 would indicate that the soil criterion is not sensitive or affected by that PDF. An increasing correlation as R approaches +1 indicates an increase in the soil criterion; a negative R indicates that the soil criterion will decrease as that input value increases.

As presented in Figure 6, the Spearman correlation coefficients indicate that the soil criterion is most highly sensitive to the PDFs for exposure duration and child soil ingestion rate, in equal proportions. Oral bioavailability is the next most sensitive parameter, followed by similar contributions from child surface area and child body weight. The soil criterion is relatively insensitive to the PDFs of dermal bioavailability, exposed surface area, body weight, and soil adherence factor for both children and adults. The soil criterion is most sensitive to the total exposure duration and child soil ingestion rates, because these distributions were defined as having high variability. The rank order of the Rs based on this analysis is consistent with the sensitivity of the soil criterion to age groups (e.g., child or adult), with childhood exposures influencing the soil criterion to a greater degree than adult exposures.

Figure 7 presents the proportional contributions of the exposure parameter PDFs to the total variance of the soil criterion. The proportions are calculated based on standardizing the squares of the Spearman correlation coefficients. The figure shows that the assumed total exposure duration and child soil ingestion rate each contribute about 42% to the total variance of the soil criterion. The assumed oral bioavailability contributes 13% to the total variance, while the remaining PDFs contribute only minimally to the total variance of the soil criterion.

Summary of Sensitivity Analysis The results of the sensitivity analysis indicate that the distribution of soil criteria is highly sensitive to the exposure duration, child soil ingestion rate, and oral bioavailability PDFs, with all other parameters being of lesser importance in the risk assessment. Due to the nature of the equation, the impact of the point-estimate values cannot be determined directly; instead, these values are discussed qualitatively next.

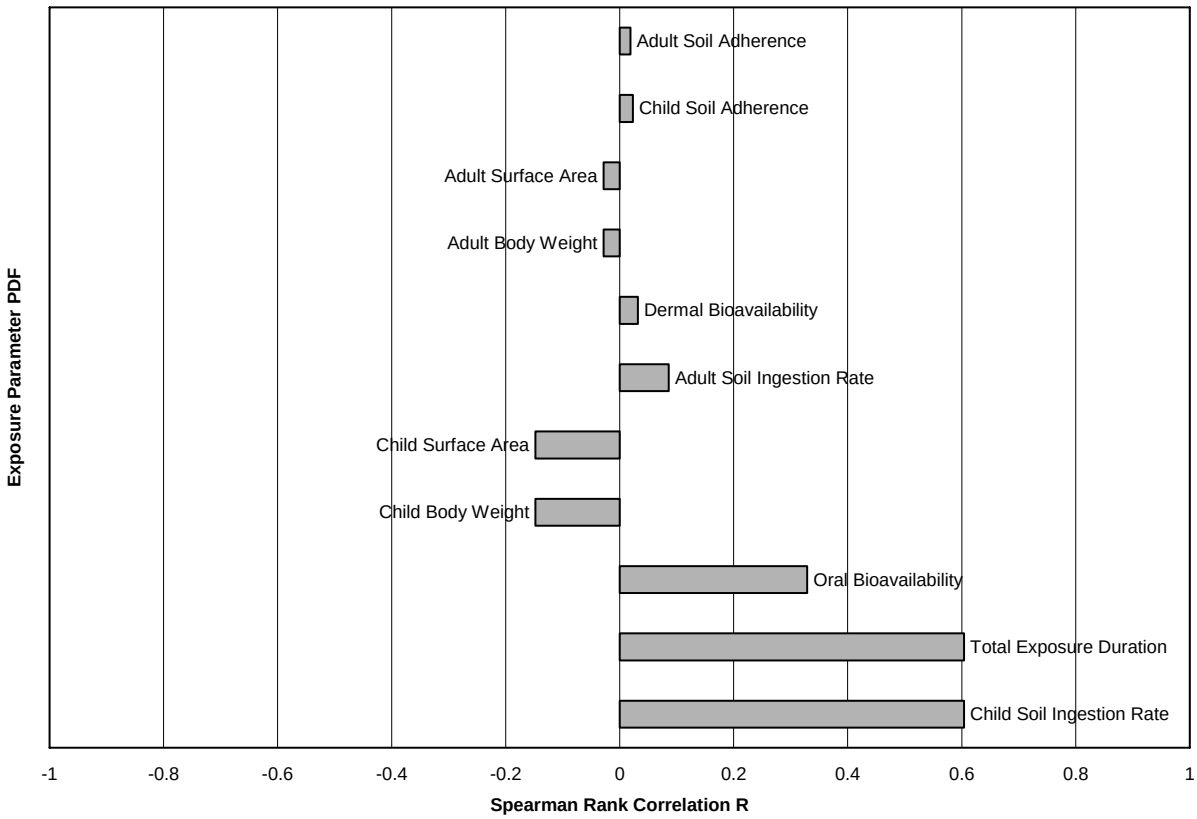

FIGURE 6. Summary of the sensitivity analysis: Spearman rank correlation of each exposure parameter for an example soil cleanup criterion at 0.7 ppb TEQ. Positive *R* values indicate the degree to which increases in the exposure parameter correlate with increases in the soil criterion. Negative *R* values indicate the degree to which increases in the exposure parameter correlate with decreases in the soil criterion.

Qualitative Uncertainty Analysis

The purpose of this subsection is to identify and qualitatively discuss the uncertainties associated with the urban residential soil criteria. As in the sensitivity analysis, we have selected the 0.7 ppb soil criterion based on cancer risk (1 in 100,000, and cancer potency of 75,000 $(mg/kg/d)^{-1}$) in order to simplify the analysis of uncertainties focused on parameters driving the LADD estimates. This places the soil criterion into perspective by describing the assumptions and uncertainties inherent in its evaluation (U.S. EPA, 1989). Incorporating the stochastic analysis decreases the overall uncertainty associated with the exposure assessment by presenting a range of representative exposure assumptions. However, the stochastic analysis does not address other uncertainties that are recognized, but not quantified, in this analysis. For example, Popp et al. (2005) review the weight of scientific evidence concerning cancer dose-response relationships for TCDD and conclude that the evidence strongly suggests that a threshold is likely to exist below which no excess cancer risk is identified. A truly "quantitative" uncertainty analysis would include this and perhaps other scientifically supported theories that could skew the current analysis considerably. We have chosen a more conservative, public health-based approach in this probabilistic risk assessment that tends to err on the side of public health protection, but that is bounded and balanced by valid scientific data and considerations to the extent possible.

Environmental Degradation Organic chemicals are naturally degraded in the environment by a variety of processes (i.e., photodegradation, microbial activity, hydrolysis, etc.). Half-lives vary for specific chemicals based on environmental conditions (i.e., presence of bacteria, pH, exposure to sunlight and oxygen). The soil criteria calculation method utilized here does not incorporate chem-

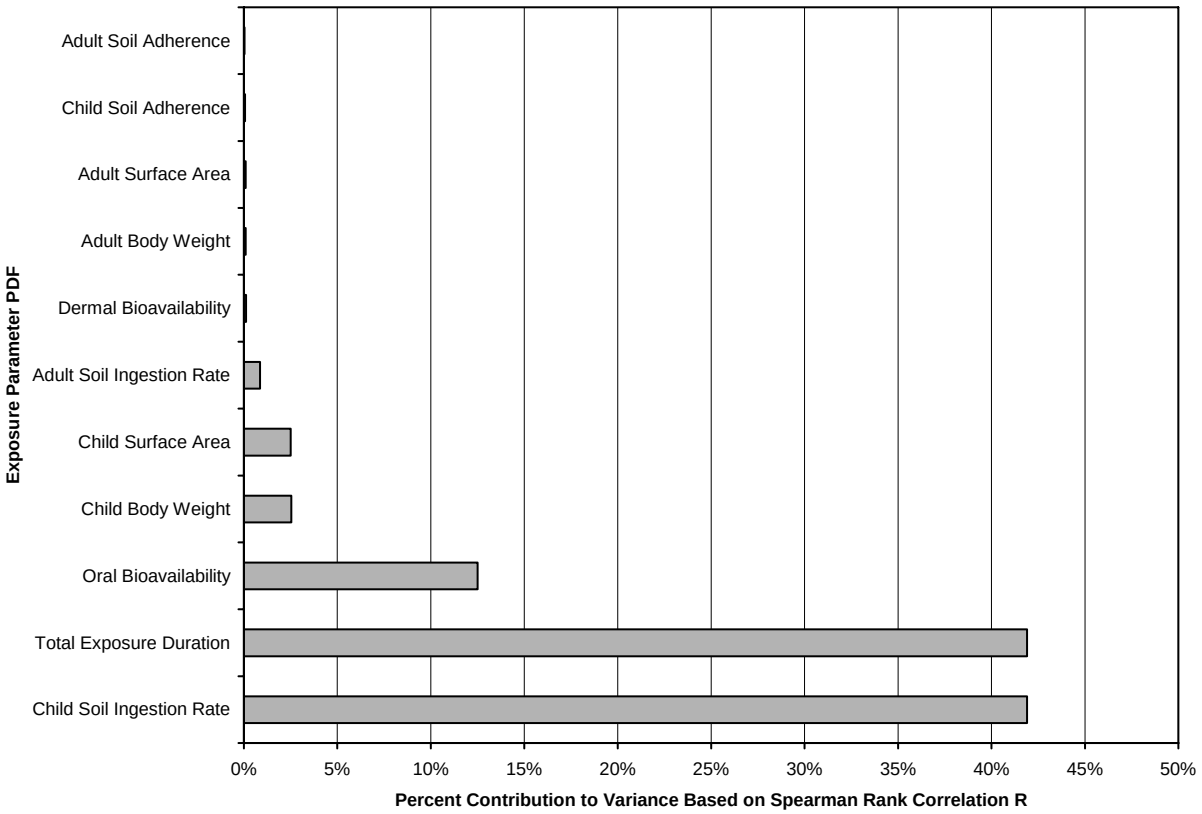

FIGURE 7. Summary of the uncertainty analysis: Contribution of each exposure parameter to the total variance for an example soil cleanup criterion at 0.7 ppb TEQ. Note that the percent contribution to total variance includes varying degrees of covariance with other exposure parameters. As a result, the sum of all values for percent contribution exceeds 100%.

ical-specific degradation (i.e., environmental half-lives) to evaluate the natural environmental degradation of the PCDD/Fs in soil. Our prior estimates of the environmental half-life of dioxin (TCDD) in soil that is more than an inch below the surface was 20–100 yr; accordingly, the rate is sufficiently low as to be negligible for purposes of most risk assessments.

However, U.S. EPA (1989) recommends incorporation of natural fate processes:

> *To determine the fate of the chemicals of potential concern at a particular site, obtain information on their physical/chemical and environmental fate properties. Use computer data bases (e.g., SRC's Environmental Fate CHEMFATE, and BIODEG data bases; BIOSIS; AQUIRE) and the open literature as necessary as sources for up-to-date information on the physical/chemical and fate properties of the chemicals of potential concern*. (p.)

Information on the rates of chemical breakdown due to the various environmental processes—including photo-oxidation, chemical reactions (e.g., hydrolysis), and microbial action—are available from a number of sources. One of the them is the U.S. EPA *Superfund Public Health Evaluation Manual* (U.S. EPA, 1986), which provides an experimentally derived half-life for TCDD in soil of 12 yr. However, this value is outdated and clearly too low for most settings; to avoid underestimating the possible degree of exposure to humans, this factor was not incorporated into the assessment.

Child Soil Ingestion Rate/Pica Behavior Long-term annual soil ingestion rates for children were used in this assessment. No attempt was made to address the small number of children who intentionally ingest larger quantities of soil, a condition known as geophagia, or pica. Pica is the intentional ingestion of non-nutritional items such as soil, cigarette butts, paint, plaster, etc. Geophagia is a specific form of pica that refers to the ingestion of soils or clay.

The occurrence of soil pica behavior in children is so infrequent that there are insufficient data with which to accurately characterize this behavior, let alone develop a scientifically defensible PDF for use in risk assessment. In the U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997a), it was noted that only one child exhibited soil pica behavior in the major studies the Agency identified to quantify children's soil ingestion rates (Binder et al., 1986; Calabrese et al., 1989a, 1989b; Clausing et al., 1987; Davis et al., 1990; van Wijnen et al., 1990). In all, these 6 studies examined the soil ingestion patterns of 632 children over a combined period of 35 d, and only one incidence of pica was noted (Calabrese et al., 1989a, 1989b). This low prevalence is consistent with the most recent soil ingestion study by Stanek et al. (1999) that failed to identify any pica behavior (Stanek et al., 1999). Further, pica behavior is thought to be a result of malnourishment and/or child neglect (children will eat soil, paint chips, etc. to supplement the minerals that are lacking in the diet), and is also thought to occur primarily in very economically depressed areas; the likelihood of these factors applying to any given urban residential site cannot be generalized (Federman et al., 1997). At one time, Paustenbach (1987) suggested that based on his reading of the literature, he expected that no more than 1 in 300 children demonstrated some tendency to eat appreciable quantities of soil and that, nearly always, these events occurred only rarely or for a short period of time during certain windows of time.

Due to the low frequency of pica behavior, elevated soil ingestion rates in children are typically discussed qualitatively (if at all) in environmental risk assessments. In fact, U.S. EPA guidance indicates that pica behavior does not need to be addressed:

> For risk assessment purposes, pica is typically defined as "an abnormally high soil ingestion rate" and is believed to be uncommon in the general population (U.S. EPA 1989f). U.S. EPA risk assessment documents do not identify a default "pica" soil ingestion rate (U.S. EPA 1989e; 1989f; 1991b). Therefore, U.S. EPA [Office of Solid Waste] does not recommend addressing pica behavior as part of [incinerator risk assessments]. (U.S. EPA, 1998, p. 6–7)

Moreover, ATSDR (2001) recently convened a soil-pica workshop that indicates the critical issues of prevalence and appropriate intake rates and frequencies for this behavior remain unresolved with respect to practical risk management applications. In summary, the available data suggest pica behavior is a rare and infrequent event, and consistent with U.S. EPA guidance, this issue is not quantitatively addressed in this assessment.

RECOMMENDATION BASED ON THE WEIGHT-OF-SCIENTIFIC EVIDENCE AND HISTORICAL PUBLIC POLICY

Over the 20 yr since the publication of Kimbrough et al. (1984), the 1 ppb guideline for dioxin TEQ in soils has frequently been used to help inform decisions about the magnitude of health risk. Since that time, thousands of toxicology, epidemiology, exposure and fate/transport studies have been conducted for this family of chemicals.

Despite all the research, considerable uncertainty remains about the human health hazards for PCDD/Fs at commonly encountered environmental exposures. From 2000 through 2005, U.S. EPA suggested that current background doses of these chemicals from meat, fish, and dairy products are near those that require regulatory attention in order to protect human health. On the other hand, some scientific and regulatory agencies, including the CDC and WHO, have concluded that current dietary exposures don't pose an appreciable health hazard; these agencies, however, urge that exposures be reduced wherever possible.

This analysis is an attempt to integrate all the relevant information that has been developed over the 20 yr since the derivation of the 1 ppb guideline (Kimbrough et al., 1984). Specifically, our analysis of the cancer risks and noncancer hazards posed by PCDD/PCDFs and the most recent information on exposure led to development of a range of soil criteria that should not pose a health risk considered worthy of concern (e.g., virtually safe) in an urban residential setting. Our probabilistic assessment allows risk managers to examine the degree of conservatism associated with varied margins of

safety at different percentiles and under a wide variety of scientific assumptions and parameters. Site-specific adjustment factors were identified that should be incorporated. As discussed previously, for those sites where contaminated soils have appreciably changed the local fish concentrations due to runoff, where cows or chickens are grazing on significantly contaminated soils, and where there continues to be a significant ongoing source of airborne release of PCDD/PCDF, this must be accounted for in the risk assessment. A sensitivity analysis, as well as a qualitative and quantitative uncertainty analysis was conducted here so the impact of alterations in key values affecting direct soil contact can be readily assessed. Our goal was to achieve a level of thoroughness and transparency that met the risk characterization guidelines suggested by NAS (1994) and other scientific or regulatory bodies.

Our analysis supports the historical position of the U.S. EPA and ATSDR that a 1 ppb dioxin TEQ soil cleanup criterion is almost certainly adequately protective for most urban residential locations for both the possible cancer and non-cancer health effects associated with exposure to PCDD/Fs (DeRosa et al., 1999a, 1999b; Fields, 1998; Pohl et al., 2002). However, our work shows that soil PCDD/F cleanup levels for the most likely residential exposures (i.e., at the 50th percentile) center around 1–5 ppb TEQ whether one focuses on the carcinogenic or noncarcinogenic hazard. For example, the range of applicable cleanup values using a uniform distribution of cancer slope factors ranging from 75,000 to 156,000 $(mg/kg/d)^{-1}$ leads to cleanup values (or guidance values) ranging from about 0.54 ppb at the 95th percentile to 3.1 ppb at the 50th percentile (Figure 8). These values are consistent with the soil cleanup guidelines proposed and/or accepted by several public health agencies in the United States and in other developed countries (Table 1).

Based on our analysis, assuming the cancer potency factor does not exceed 156,000 $(mg/kg/d)^{-1}$ and that new information on developmental toxicity is not markedly different from what is currently

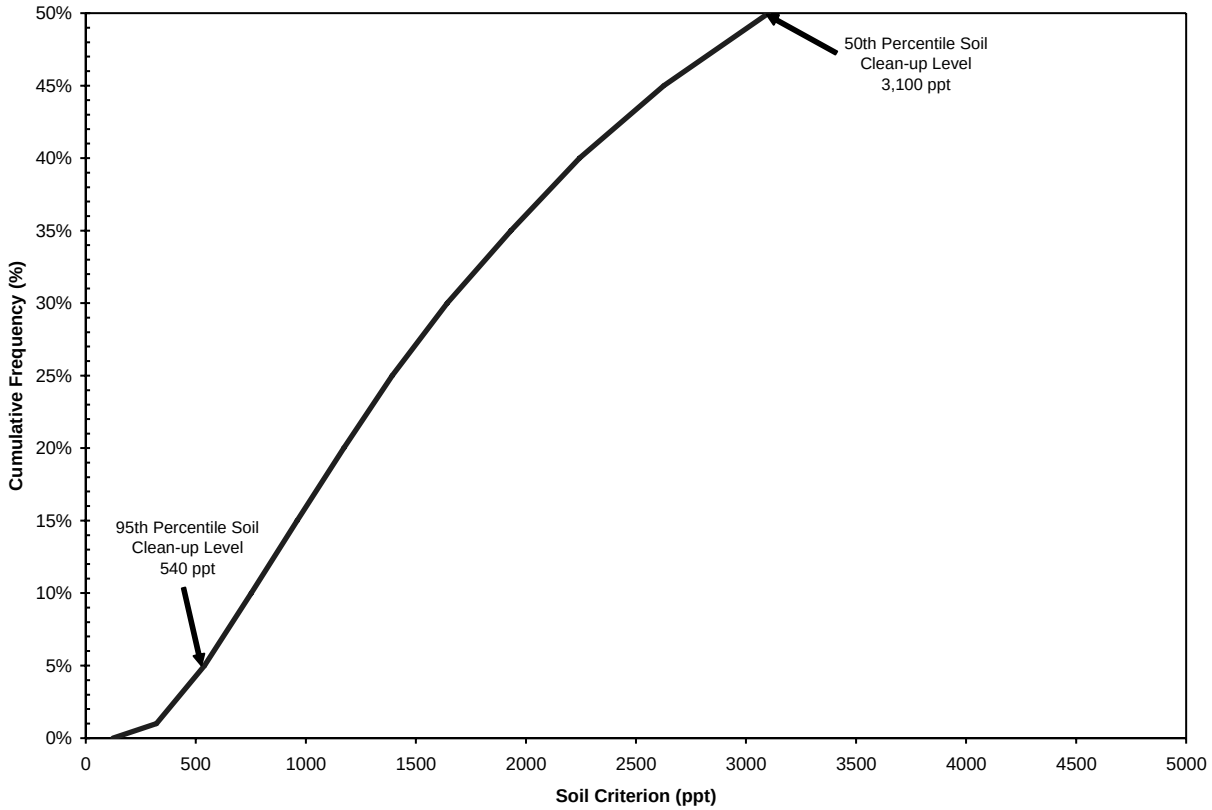

FIGURE 8. Cumulative frequency distribution for 2,3,7,8-TCDD soil cleanup criterion using a uniform cancer potency from 9600 to 156,000 per mg/kg/d. Note that, about 95% of the population has a cancer risk below 1 per 100,000 at 540 ppt TEQ based on this analysis.

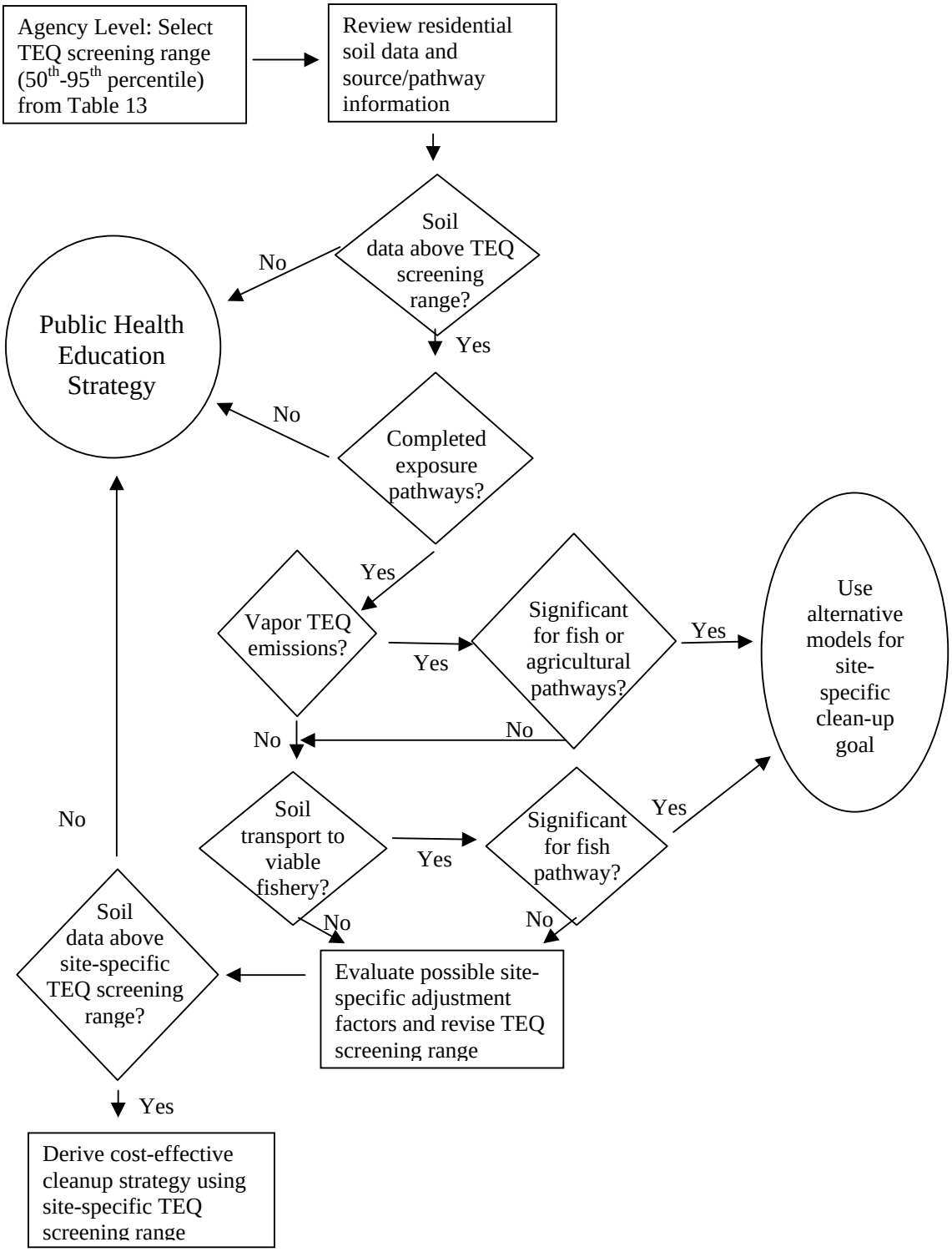

FIGURE 9. Suggested decision tree for evaluating applicability of the calculated soil cleanup criteria. Adapted from a draft decision tree developed by ATSDR.

understood, soil cleanup criteria or guidelines ranging from 0.4 to 1.1 ppb TEQ should be considered adequately protective of human health at the 95th percentile. Site-specific adjustment factors may justify several-fold higher values that would be equally protective. This level of protection (at the 95th percentile) is consistent with the goals of most public health agencies. However, if the U.S. EPA proposed cancer potency factor of 1,000,000 were to be considered appropriate, then current urban background concentrations (e.g., about 5–50 ppt TEQ) could be considered the target value.

Considering the background intake of PCDD/Fs in the diet, persons living in communities which have soil concentrations in the vicinity of 0.5 to 1 ppb should not have blood levels of these chemicals markedly different from those in the general population. For example, ATSDR did not detect increased blood TEQs in its evaluations of the blood of persons who live in communities that had PCDD/F contaminated soils at concentrations that averaged less than 1 ppb (Susten, 2004). Moreover, the ATSDR site-specific health assessment teams often advised state agencies, particularly in U.S. EPA Region 7, that under most residential soil exposure scenarios, soil dioxin TEQ levels (i.e., total TEQs) not uniformly greater than 1 ppb were unlikely to pose a health threat (Susten, 2004). Further, the ATSDR (1997a, 1997b) Interim Policy Guidelines and Technical Support Document on Dioxin and Dioxin-like Compounds in Soil (announced in the *Federal Register* 62(152):42558–42559, August 7, 1997) support regulatory use of the 1 ppb action level; these documents define the official agency policy to date. The relationship between soil and housedust concentrations of dioxins versus changes in blood levels is currently being evaluated by the University of Michigan for the city of Midland, MI, and the results could have a profound impact on this issue (University of Michigan, 2005).

Figure 9 depicts a decision-tree approach that may assist risk managers in evaluating the applicability of these soil clean-up criteria and in identifying issues that may require alternative approaches on a site-specific basis. In all cases, reliance on a single upper bound cleanup value from Tables 13 and 14 should be avoided, and concerned risk managers should understand the underlying conservative risk assessment methods used and proper interpretations of the full range of percentiles shown, that is, best estimate (50th percentile) through conservative maximum reasonable exposure (e.g., 95th percentile). This should assist in avoiding the mistaken impression that exceeding the selected soil cleanup levels by a small margin poses some risk of overt toxicity, cancer, or some other adverse effect.

Further, a number of ongoing scientific debates and developing research may influence the agency's or risk manager's decision on appropriate soil criteria to choose from Tables 13 and 14. Resolutions to the debates about appropriate potency factors, the importance of the new NTP (2004) bioassay findings, and new data and interpretations regarding appropriate RfDs applicable to risk assessment are expected to be forthcoming. These issues will likely influence both the scientific consensus and possibly science policy decisions regarding PCDD/F risk assessment in the near future.

And finally, the research and debate continues regarding importance of the Ah receptor on toxicity and how to predict the actual hazard at low doses and at the body burdens present in the general population. In the future, when estimating risk, it may well become standard practice to account for the presence of the multiple known ligands other than PCDD/Fs which are present in the normal diet and the uncertain dose-response relationship for Ah receptor binding affinity. Depending on how the various scientific and regulatory bodies choose to incorporate these factors into their decision making, future decisions regarding the health significance of PCDD/Fs in soils or other media will likely be quite different than they are today.

REFERENCES

Adami, H. O., Cole, P., Mandel, J. S., Pastides, H., Starr, T., and Trichopoulos, D. 2000. *Dioxin and cancer*. Paper read at Chlorine Chemistry Council Sponsored Dioxin Workshop, International Society of Regulatory Toxicology and Pharmacology and American Bar Association. www.dioxinfacts.org/dioxin_health/public_policy/dr.pdf.

Adami, H. O., Day, N. E., Trichopoulos, D., and Willett, W. C. 2001. Primary and secondary prevention in the reduction of cancer morbidity and mortality. *Eur. J. Cancer* 37:S118–S127.

AEA Technology. 1999. *Compilation of European Union dioxin exposure and health data: Task 1—Member state legislation and programmes*. Report for the European Commission DG Environment and the United Kingdom Department of the Environmental, Transport and Regions. www.mfe.govt.nz/publications/hazardous/taranaki-dioxin-report-sep02/appendix-d-sep02.pdf.

Agency for Toxic Substances and Disease Registry. 1992. *Toxicological profile for chlorinated dibenzo-*p*-dioxins*. Atlanta, GA: ATSDR.

Agency for Toxic Substances and Disease Registry. 1997a. *Interim policy guideline: Dioxin and dioxin-like compounds in soil*. Atlanta, GA: ATSDR.

Agency for Toxic Substances and Disease Registry. 1997b. *Technical support document for ATSDR interim policy guideline: Dioxin and dioxin-like compounds in soil*. Atlanta, GA: ATSDR.

Agency for Toxic Substances and Disease Registry. 1998. *Toxicological profile for chlorinated dibenzo-*p*-dioxins*. Atlanta, GA: ATSDR. (Update).

Agency for Toxic Substances and Disease Registry. 2005. *Updated ATSDR policy guidelines for dioxin and dioxin-like compounds in soil, draft*, November 9, 2004. Presented at joint public meeting of the Board of Scientific Counselors, National Center for Environmental Health and ATSDR November 18–19. Available from ATSDR, Atlanta, GA.

Ahlborg, U., Hakansson, H., Wern, F., and Hanberg, A. 1988. Nordisk Dioxinrisk bedornning. Rapport fran en expertgroup. *Nord* 4:9. (Miljorapport):7 (Kobenhavn: Nordisk Ministerrad).

Assennato, G., Cervino, D., Emmett, E. A., Longo, G., and Merlo, F. 1989. Follow-up of subjects who developed chloracne following TCDD exposure at Seveso. *Am. J. Ind. Med.* 16:119–125.

ATSDR Agency for Toxic Substances and Disease Registry. 2001. *Summary Report for the ATSDR Soil-Pica Workshop*. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Aylward, L. L., and Hays, S. M. 2002. Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels. *J. Expos. Anal. Environ. Epidemiol.* 12:319–328.

Aylward, L. L., Brunet, R. C., Starr, T., Delzell, E., Cheng, H., and Beall, C. 2004. Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. *Organohalogen Compounds* 66:3394–3401.

Aylward, L. L., Brunet, R. C., Carrier, G., Hays, S. M., Cushing, C. A., Needham, L. L., Patterson, D. G., Jr., Gerthoux, P. M., Brambilla, P., and Mocarelli, P. 2005a. Concentration-dependent TCDD elimination kinetics in humans: Toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. *J. Expos. Anal. Environ. Epidemiol.* 15:51–65.

Aylward, L. L., Brunet, R. C., Starr, T., Carrier, G., Delzell, E., Cheng, H., and Beall, C. 2005b. Exposure reconstruction for the TCDD exposed NIOSH cohort using a concentration- and age-dependent model of elimination. *Risk Anal*. in press.

Aylward, L. L., Lamb, J. C., and Lewis, S. C. 2005c. Issues in risk assessment for developmental effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds. *Toxicol. Sci.* 87:3–10.

Baccarelli, A., Pesatori, A. C., Consonni, D., Mocarelli, P., Patterson, D. G., Jr., Caporaso, N. E., Bertazzi, P. A., and Landi, M. T. 2005. Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. *Br. J. Dermatol.* 152:459–465.

Banks, Y. B., and Birnbaum, L. S. 1991. Absorption of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) after low dose dermal exposure. *Toxicol. Appl. Pharmacol.* 107:302–310.

Bannister, R., Davis, D., Zacharewski, T., Tizard, I., and Safe, S. 1987. Aroclor 1254 as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist: Effects on enzyme induction and immunotoxicity. *Toxicology* 46:29–42.

Bannister, R., Biegel, L., Davis, D., Astroff, B., and Safe, S. 1989. 6-Methyl-1,3,8-trichlorodibenzofuran (MCDF) as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist in C57BL/6 mice. *Toxicology* 54:139–150.

Becher, H., Steindorf, K., and Flesch-Janys, D. 1998. Quantitative cancer risk assessment for dioxins using an occupational cohort. *Environ. Health Perspect.* 106:663–670.

Bertazzi, P. A., Pesatori, A. C., and Zocchetti, C. 1998. [Seveso. Dioxin: an example of environmental medicine. Epidemiologic data as guidelines for health programming]. *G. Ital. Med. Lav. Ergon.* 20:194–196.

Biegel, L., Harris, M., Davis, D., Rosengren, R., Safe, L., and Safe, S. 1989. 2,2′,4,4′,5,5′-Hexachlorobiphenyl as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist in C57BL/6J mice. *Toxicol. Appl. Pharmacol.* 97:561–571.

Binder, S., Sokal, D., and Maughan, D. 1986. Estimating soil ingestion: the use of tracer elements in estimating the amount of soil ingested by young children. *Arch. Environ. Health* 41:341–345.

Birnbaum, L. S., and Couture, L. A. 1988. Disposition of octachlorodibenzo-*p*-dioxin (OCDD) in male rats. *Toxicol. Appl. Pharmacol.* 93:22–30.

BMU. 1999. German Federal Soil Protection and Contaminated Sites Ordinance. Federal Environment Ministry, Nature Conservation and Nuclear Safety (BMU). www.bmu.de/english/aktuell/4152.php.

Bodner, K. M., Collins, J. J., Bloemen, L. J., and Carson, M. L. 2003. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Occup. Environ. Med.* 60:672–675.

Bonaccorsi, A., di Domenico, A., Fanelli, R., Merli, F., Motta, R., Vanzati, R., and Zapponi, G. A. 1984. The influence of soil particle adsorption on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin biological uptake in the rabbit. *Arch. Toxicol. Suppl.* 7:431–434.

Boyce, C. 1998. Comparison of approaches for developing distributions for carcinogenic slope factors. *Hum. Ecol. Risk Assess.* 42:527–577.

Brainard, J., and Burmaster, D. E. 1992. Bivariate distributions for height and weight of men and women in the United States. *Risk Anal.* 12:267–275.

Brunekreef, B., Noy, D., Biersteker, K., and Boleij, J. 1983. Blood lead levels of Dutch city children and their relationship to lead in the environment. *J. Air Pollut. Control Assoc.* 33:872–876.

Bukowski, J., Korn, L., and Wartenberg, D. 1995. Correlated inputs in quantitative risk assessment: The effects of distributional shape. *Risk Anal.* 18:215–219.

Burmaster, D. E. 1998. Lognormal distributions for total water intake and tap water intake by pregnant and lactating women in the United States. *Risk Anal.* 18:215–219.

Burmaster, D. E. 1999. Lognormal distributions for skin area as a function of body weight. *Risk Anal.* 18:27–32.
Burmaster, D. E., and Crouch, E. A. 1997. Lognormal distributions for body weight as a function of age for males and females in the United States, 1976–1980. *Risk Anal.* 17:499–505.
Burmaster, D. E., and Harris, R. H. 1993. The magnitude of compounding conservatisms in Superfund risk assessments. *Risk Anal.* 13:131–134.
Calabrese, E. J. 2002. Hormesis: Changing view of the dose-response, a personal account of the history and current status. *Mutat. Res.* 511:181–189.
Calabrese, E. J., and Baldwin, L. A. 2001a. The frequency of U-shaped dose responses in the toxicological literature. *Toxicol. Sci.* 62:330–338.
Calabrese, E. J., and Baldwin, L. A. 2001b. Scientific foundations of hormesis. *Crit. Rev. Toxicol.* 31:4–5.
Calabrese, E. J., and Baldwin, L. A. 2002. Defining hormesis. *Hum. Exp. Toxicol.* 21:91–97.
Calabrese, E. J., and Stanek, E. J. 1991. A guide to interpreting soil ingestion studies. II. Qualitative and quantitative evidence of soil ingestion. *Regul. Toxicol. Pharmacol.* 13:278–292.
Calabrese, E. J., and Stanek, E. J. 1992. What proportion of household dust is derived from outdoor soil? *J. Soil Contam.* 1:253–263.
Calabrese, E. J., and Stanek, E. J. 1995. Resolving intertracer inconsistencies in soil ingestion estimation. *Environ. Health Perspect.* 103:454–457.
Calabrese, E. J., Kostecki, P. T., and Gilbert, C. E. 1987. How much soil do children eat? An emerging consideration for environmental health risk assessment. *Comm. Toxicol*. as cited in U.S. EPA (1997a).
Calabrese, E. J., Barnes, R., Stanek, E. J., Pastides, H., Gilbert, C. E., Veneman, P., Wang, X. R., Lasztity, A., and Kostecki, P. T. 1989a. How much soil do young children ingest: An epidemiologic study. *Regul. Toxicol. Pharmacol.* 10:123–137.
Calabrese, E. J., Pastides, H., Barnes, R., Edwards, C., and Kostecki, P. T. 1989b. How much soil do young children ingest: An epidemiologic study. In *Petroleum contaminated soils.* pp. Chelsea, MI: Lewis.
Calabrese, E. J., Stanek, E. J., Gilbert, C. E., and Barnes, R. M. 1990. Preliminary adult soil ingestion estimates: results of a pilot study. *Regul. Toxicol. Pharmacol.* 12:88–95.
Calabrese, E. J., Stanek, E. J., James, R. C., and Roberts, S. M. 1997a. Soil ingestion: A concern for acute toxicity in children. *Environ. Health Perspect.* 105:1354–1358.
Calabrese, E. J., Stanek, E. J., Pekow, P., and Barnes, R. M. 1997b. Soil ingestion estimates for children residing on a Superfund site. *Ecotoxicol. Environ. Safety.* 36:258–268.
Calabrese, E. J., Stanek, E. J., Barnes, R., Burmaster, D. E., Callahan, B. G., Heath, J. S., Paustenbach, D. J., Abraham, J., and Gephart, L. A. 1996. Methodology to estimate the amount and particle size of soil ingested by children: implications for exposure assessment at waste sites. *Regul. Toxicol. Pharmacol.* 24:264–268.
Calabrese, E. J., Stanek, E. J., Barnes, R., Burmaster, D. E., Callahan, B. G., Heath, J. S., Paustenbach, D., Abraham, J., and Gephart, L. A. 1997c. Methodology to estimate the amount and particle size of soil ingested by children: Implications for exposure assessment at waste sites. *Regul. Toxicol. Pharmacol.* 2:264–268. erratum in *Regul. Toxicol Pharmacol* 25:87.
Caramaschi, F., del Corno, G., Favaretti, C., Giambelluca, S. E., Montesarchio, E., and Fara, G. M. 1981. Chloracne following environmental contamination by TCDD in Seveso, Italy. *Int. J. Epidemiol.* 10:135–143.
CCME. 2001. *Canadian soil quality guidelines for the protection of environmental and human health; Polychlorinated dibenzo*-p-*dioxins and polychlorinated dibenzofurans (PCDD/Fs)*. Canadian Environmental Quality Guidelines, Canadian Council of Ministers of the Environment. http://www.ccme.ca/publications.
Chen, C.Y., Hamm, J. T., Hass, J. R., and Birnbaum, L. S. 2001. Disposition of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and non-*ortho* polychlorinated biphenyls in pregnant Long Evans rats and the transfer to offspring. *Toxicol. Appl. Pharmacol.* 173:65–88.
Clausing, P., Brunekreef, B., and van Wijnen, J. H. 1987. A method for estimating soil ingestion by children. *Int. Arch. Occup. Environ. Health* 59:73–82.
Cocucci, S., Di Gerolamo, F., Verderio, A., Cavallaro, A., Colli, G., Gorni, A., Vernizzi, G., and Luciani, L. 1979. Absorption and translocation of tetrachlorodibenzo-*p*-dioxin by plants from polluted soil. *Experientia* 35:482–484.
Cohen, J. T., Beck, B. D., and Rudel, R. 1997. Life years lost at hazardous waste sites: remediation worker fatalities vs. cancer deaths to nearby residents. *Risk Anal.* 17:419–425.
Cole, P., Trichopoulos, D., Pastides, H., Starr, T., and Mandel, J. S. 2003. Dioxin and cancer: A critical review. *Regul. Toxicol Pharmacol.* 38:378–388.
Connor, K., and Aylward, L. L. 2005. Human response to dioxin: Aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. *J. Toxicol. Environ. Health B,* in press.
Connor, K., Harris, M., Edwards, C., Chu, A., Clark, G., and Finley, B. 2004. Estimating the total TEQ in human blood from naturally-occurring vs. anthropogenic dioxins: a dietary study. *Organohalogen Compounds* 66:3408–3413.
Cook, P. M., Walker, M. K., Kuehl, D. W., and Peterson, R. E. 1991. *Bioaccumulation and toxicity of* 2,3,7,8-*tetrachlorodibenzo*-p-*dioxin and related compounds in aquatic ecosystems*. Madison, WI, and Duluth, MN: U.S. Environmental Protection Agency, Environmental Research Laboratory, Duluth Min, and School of Pharmacy and Environmental Toxicology Center, University of Wisconsin.
Copeland, T. L., Paustenbach, D. J., Harris, M. A., and Otani, J. 1993. Comparing the results of a Monte Carlo analysis with EPA's reasonable maximum exposed individual (RMEI): A case study of a former wood treatment site. *Regul. Toxicol. Pharmacol.* 18:275–312.
Copeland, T. L., Holbrow, A. M., Otani, J. M., Connor, K. T., and Paustenbach, D. J. 1994. Use of probabilistic methods to understand the conservatism in California's approach to assessing health risks posed by air contaminants. *J. Air Waste Manage. Assoc.* 44:1399–1413.
Costeff, H. 1966. A simple empirical formula for calculating approximate surface area in children. *Arch. Dis. Child.* 41:681–683.

CoT. 2001. *Committee on Toxicity and Chemicals in Food, Consumer Products and the Environment, statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls*. United Kingdom. Committee on Toxicity. COT/2001/07. October 2001. http://www.food.gov.uk/science/ouradvisors/toxicity/statements/cotstatements2001/dioxinsstate.

Courval, I. M., DeHoog, I. V., Holzman, C. B., Tay, E. M., Fischer, L., Humphrey, H. E., Paneth, N. S., and Sweeney, A. M. 1996. Fish consumption and other characteristics of reproductive-aged Michigan anglers—a potential population for studying the effects of consumption of Great Lakes fish on reproductive health. *Toxicol. Ind. Health* 12(3-4):347–359.

Crouch, E. A., Kirman, C. R., Aylward, L. L., Budinsky, B. D., Landenberger, B. D., and Long, T. F. 2005. Incorporating probabilistic carcinogenicity assessment in health risk assessment. *Toxicol. Sci.* 84:79–80.

Crump, K. S., Canady, R., and Kogevinas, M. 2003. Meta-analysis of dioxin cancer dose response for three occupational cohorts. *Environ. Health Perspect.* 111:681–687.

Davis, D., and Safe, S. 1989. Dose-response immunotoxicities of commercial polychlorinated biphenyls (PCBs) and their interaction with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicol. Lett.* 48:35–43.

Davis, D., and Safe, S. 1990. Immunosuppressive activities of polychlorinated biphenyls in C57BL/6N mice: structure–activity relationships as Ah receptor agonists and partial antagonists. *Toxicology* 63:97–111.

Davis, S., Waller, P., Buschbom, R., Ballou, J., and White, P. 1990. Quantitative estimates of soil ingestion in normal children between the ages of 2 and 7 years: Population-based estimates using aluminum, silicon, and titanium as soil tracer elements. *Arch. Environ. Health* 45:112–122.

DeCaprio, A. P., McMartin, D. N., O'Keefe, P. W., Rej, R., Silkworth, J. B., and Kaminsky, L. S. 1986. Subchronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the guinea pig: Comparisons with a PCB-containing transformer fluid pyrolysate. *Fundam. Appl. Toxicol.* 6:454–463.

Decisioneering. 2005. *Crystal ball.* Decisioneering: Inc., Denver, CO.

De Rosa, C. T., Brown, D., Dhara, R., Garrett, W., Hansen, H., Holler, J., Jones, D., Jordan-Izaguirre, D., O'Connor, R., Pohl, H., and Xintaras, C. 1997a. Dioxin and dioxin-like compounds in soil, Part I: ATSDR interim policy guideline. Agency for Toxic Substances and Disease Registry. *Toxicol. Ind. Health* 13:759–768.

De Rosa, C. T., Brown, D., Dhara, R., Garrett, W., Hansen, H., Holler, J., Jones, D., Jordan-Izaguirre, D., O'Connor, R., Pohl, H., and Xintaras, C. 1997b. Dioxin and dioxin-like compounds in soil, Part II: Technical support document for ATSDR interim policy guideline. *Toxicol. Ind. Health* 13:769–804.

De Rosa, C. T., Brown, D., Dhara, R., Garrett, W., Hansen, H., Holler, J., Jones, D., Jordan-Izaguirre, D., O'Conner, R., Pohl, H., and Xintaras, C. 1999a. Dioxin and dioxin-like compounds in soil, Part I: ATSDR policy guideline. *Toxicol. Ind. Health* 15:552–557.

De Rosa, C. T., Brown, D., Dhara, R., Garrett, W., Hansen, H., Holler, J., Jones, D., Jordan-Izaguirre, D., O'Conner, R., Pohl, H., and Xintaras, C. 1999b. Dioxin and dioxin-like compounds in soil, Part II: Technical support document for ATSDR policy guideline. *Toxicol. Ind. Health* 15:558–576.

di Domenico, A. 1990. Guidelines for the definition of environmental action alert thresholds for polychlorodibenzodioxins and polychlorodibenzofurans. *Regul. Toxicol. Pharmacol.* 11:8–23.

Diliberto, J. J., Jackson, J. A., and Birnbaum, L. S. 1996. Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) disposition following pulmonary, oral, dermal, and parenteral exposures to rats. *Toxicol. Appl. Pharmacol.* 138:158–168.

Dutch State Institute of National Health. 1982. *Evaluation of carcinogenicity and mutagenicity of 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (TCDD): Classification of "no-effect-level".* Bilthoven, the Netherlands.

Emond, C., Michaelek, J. E., Birnbaum, L. S., and DeVito, M. J. 2004. Use of a PBPK model with dose-dependent elimination rates predicts higher peak dioxin exposure than previously estimated. *Organohalogen Compounds* 66:2655–2659.

Environmental Agency Japan. 1997. *Report of Ad Hoc Committee on Dioxin Risk Assessment* (Summary in English). http://www.chem.unep.ch/pops/POPs_Inc/proceedings/bangkok/KIMURA.html.

European Commission Scientific Committee on Food. 2001. *Opinion of the scientific committee on food on the risk assessment of dioxins and dioxin-like food*. Brussels: Health and Consumer Protection Directorate General. CS/CNTM/DIOXIN/20final. http://europa.eu.int/comm/food/fs/sc/scf/reports_en.html.

Evans, J. S., Graham, J. D., Gray, G. M., and Sielken, R. L., Jr. 1994a. A distributional approach to characterizing low-dose cancer risk. *Risk Anal.* 14:25–34.

Evans, J. S., Gray, G. M., Sielken, R. L., Jr., Smith, A. E., Valdez-Flores, C., and Graham, J. D. 1994b. Use of probabilistic expert judgment in uncertainty analysis of carcinogenic potency. *Regul. Toxicol. Pharmacol.* 20:15–36.

Faqi, A. S., and Chahoud, I. 1998. Antiestrogenic effects of low doses of 2,3,7,8-TCDD in offspring of female rats exposed throughout pregnancy and lactation. *Bull. Environ. Contam. Toxicol.* 61:462–469.

Faqi, A. S., Dalsenter, P. R., Merker, H. J., and Chahoud, I. 1998. Reproductive toxicity and tissue concentrations of low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male offspring rats exposed throughout pregnancy and lactation. *Toxicol. Appl. Pharmacol.* 150:383–392.

Faust, J. B., and Zeise, L. 2004. *A reassessment of the carcinogenic potency of 2,3,7,8-tetrachlorodibenzo-p-dioxin based upon a recent long-term study in female rats*. Proceedings of the Society for Risk Analysis Annual Meeting, December.

Federman, D. G., Kirsner, R. S., and Federman, G. S. 1997. Pica: Are you hungry for the facts? *Conn. Med.* 61:207–209.

Feeley, M., and Brouwer, A. 2000. Health risks to infants from exposure to PCBs, PCDDs and PCDFs. *Food Addit. Contam.* 17:325–333.

Fehling, K. A., Ruby, M. V., and Paustenbach, D. J. 2001. In vitro bioaccessibility study of low concentrations (50–350 ppt) TEQ of dioxins/furans in weathered soils. *Organohalogen Compounds* 52:180–184.

Fields, T. 1998. *Approach for addressing dioxin in soil at CERCLA and RCRA sites.* Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. 4–26. OSWER Directive 9200.

Fingerhut, M. A., Halperin, W. E., Marlow, D. A., Piacitelli, L. A., Honchar, P. A., Sweeney, M. H., Greife, A. L., Dill, P. A., Steenland, K., and Suruda, A. J. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *N. Engl. J. Med.* 324:212–218.

Finley, B., and Paustenbach, D. 1990. Using risk assessment to design cost effective remedial investigations: A case study. *ECON (Environmental Contractor Magazine)* 5:57–59.

Finley, B., and Paustenbach, D. 1994. The benefits of probabilistic exposure assessment: Three case studies involving contaminated air, water, and soil. *Risk Anal.* 14:53–73.

Finley, B., Proctor, D., Scott, P., Harrington, N., Paustenbach, D., and Price, P. 1994. Recommended distributions for exposure factors frequently used in health risk assessment. *Risk Anal.* 14:533–553.

Finley, B. L., Connor, K. T., and Scott, P. K. 2003. The use of toxic equivalency factor distributions in probabilistic risk assessments for dioxins, furans, and PCBs. *J. Toxicol. Environ. Health A* 66:533–550.

Flesch-Janys, D., Becher, H., Gurn, P., Jung, D., Konietzko, J., Manz, A., and Papke, O. 1996. Elimination of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in occupationally exposed persons. *J. Toxicol. Environ. Health* 47:363–378.

Flesch-Janys, D., Steindorf, K., Gurn, P., and Becher, H. 1998. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ. Health Perspect.* 106:655–662.

Florida Department of Environmental Protection. 2005. *Cleanup target levels.* Tallahassee, FL. Chapter 62–77.

Gaylor, D. W., and Aylward, L. L. 2004. An evaluation of benchmark dose methodology for non-cancer continuous-data health effects in animals due to exposures to dioxin (TCDD). *Regul. Toxicol Pharmacol* 40:9–17.

Gehrs, B. C., and Smialowicz, R. J. 1997. Alterations in the developing immune system of the F 344 rat after perinatal exposure to 2.3,7,8-tetrachlorodibenzo-*p*-dioxin. I. Effects on the fetus and the neonate. *Toxicology* 122:219–228.

Gehrs, B. C., Riddlge, M. M., Williams, W. C., and Smialowicz, R. J. 1997. Alterations in the developing immunce system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. II. Effects on the pup and the adult. *Toxicology* 122:229–240.

Gephart, L. A., Tell, J. G., and Triemer, L. R. 1994. Exposure factors manual. *J. Soil Contam.* 3:47–117.

Geyer, H. J., Schramm, K. W., Feicht, E. A., Behechti, A., Steinberg, C., Bruggemann, R., Poiger, H., Henkelmann, B., and Kettrup, A. 2002. Half-lives of tetra-, penta-, hexa-, hepta-, and octachlorodibenzo-*p*-dioxin in rats, monkeys, and humans—A critical review. *Chemosphere* 48:631–644.

Goeden, H. M., and Smith, A. H. 1989. Estimation of human exposure from fish contaminated with dioxins and furans emitted by a resource-recovery facility. *Risk Anal.* 9:377–383.

Goodman, D. G., and Sauer, R. M. 1992. Hepatotoxicity and carcinogenicity in female Sprague-Dawley rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): A pathology working group reevaluation. *Regul. Toxicol. Pharmacol.* 15:245–252.

Gough, M. 1988. Science policy choices and the estimation of cancer risk associated with exposure to TCDD. *Risk Anal.* 8:337–342.

Gough, M. 1991. Human exposures from dioxin in soil—A meeting report. *J. Toxicol. Environ. Health* 32:205–235.

Gough, M. 2003. The limits of science: dioxin. *Regul. Toxicol. Pharmacol.* 37:170–171.

Gray, L. E., Ostby, J. S., and Kelce, W. R. 1997a. A dose-response analysis of the reproductive effects of a single gestational dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male Long Evans Hooded rat offspring. *Toxicol. Appl. Pharmacol.* 146:11–20.

Gray, L. E., Wolf, C., Mann, P., and Ostby, J. S. 1997b. In utero exposure to low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin alters reproductive development of female Long Evans hooded rat offspring. *Toxicol. Appl. Pharmacol.* 146:237–244.

Greene, J. F., Hays, S., and Paustenbach, D. 2003. Basis for a proposed reference dose (RfD) for dioxin of 1–10 pg/kg-day: A weight of evidence evaluation of the human and animal studies. *J. Toxicol. Environ. Health B* 6:115–159.

Haas, C. N., Kersten, S. P., Wright, K., Frank, M. J., and Cidambi, K. 1997. Generalization of independent response model for toxic mixtures. *Chemosphere* 34:699–710.

Hamed, M. M., and Bedient, P. B. 1997. On the effect of probability distributions of input variables in public health risk assessment. *Risk Anal.* 17:97–105.

Harper, N., Connor, K., Steinberg, M., and Safe, S. 1995. Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: Nonadditive (antagonistic) interactions. *Fundam. Appl. Toxicol.* 27:131–139.

Hartley, H. O., and Sielken, R. L., Jr. 1977. Estimation of "safe doses" in carcinogenic experiments. *Biometrics* 33:1–30.

Hattis, D., and Burmaster, D. E. 1994. Assessment of variability and uncertainty distributions for practical risk analysis. *Risk Anal.* 14:713–730.

Hawley, J. K. 1985. Assessment of health risk from exposure to contaminated soil. *Risk Anal.* 5:289–302.

Haws, L., Harris, M., Su, S., Birnbaum, L., DeVito, M. J., Farland, W., Walker, N., Connor, K., Santamaria, A., and Finley, B. 2004. Development of a refined database of relative potency estimates to facilitate better characterization of variability and uncertainty in the current mammalian TEFs for PCDDs, PCDFs and dioxin-like PCBs. *Organohalogen Compounds* 66:3426–3432.

Hays, S., Aylward, L. L., Finley, B., and Paustenbach, D. 2001. Implementing a cancer risk assessment for dioxin using a margin of exposure approach and an internal measure of dose. *Organohalogen Compounds* 53:225–228.

Health Council of the Netherlands. 1996. *Health Council of the Netherlands Committee on the Risk Evaluation of Substances/Dioxins. Dioxins, polychlorinated dibenzo*-p-*dioxins dibenzofurans and dioxin-like polychlorinated biphenyls.* Rijswijk: Health Council of the Netherlands. Publication no. 1996/10E.

Hirschhorn, J. S. 1997. Cleanup levels for dioxin-contaminated soils. *Remediation* 7:63–80.

Hoffman, F. O., and Hammonds, J. S. 1994. Propagation of uncertainty in risk assessments: the need to distinguish between uncertainty due to lack of knowledge and uncertainty due to variability. *Risk Anal.* 14:707–712.

Holmes, K. K., Jr., Shirai, J. H., Richter, K. Y., and Kissel, J. C. 1999. Field measurement of dermal soil loadings in occupational and recreational activities. *Environ. Res.* 80:148–157.

Hulster, A., Muller, J. F., and Marschner, H. 1994. Soil plant transfer of polychlorinated dibenzo-p-dioxins and dibenzofurans to vegetables of the cucumber family (*Cucurbitaceae*). *Environ. Sci. Technol.* 28(6):1110–1115.

Hurst, C. H., DeVito, M. J., Setzer, R. W., and Birnbaum, L. S. 2000a. Acute administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in pregnant Long Evans rats: Association of measured tissue concentrations with developmental effects. *Toxicol. Sci.* 53:411–420.

Hurst, C. H., DeVito, M. J., and Birnbaum, L. S. 2000b. Tissue disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in maternal and developing Long Evans rats following subchronic exposure. *Toxicol. Sci.* 57:275–283.

IARC. 1997. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. *IARC Monogr. Eval. Carcinogen. Risks Hum.* 69:1–631.

Ideo, G., Bellati, G., Bellobuono, A., and Bissanti, L. 1985. Urinary D-glucaric acid excretion in the Seveso area, polluted by tetrachlorodibenzo-*p*-dioxin (TCDD): five years of experience. *Environ. Health Perspect.* 60:151–157.

Johnson, T., and Capel, J. 1992. *A Monte Carlo approach to simulating residential occupancy periods and its application to the general U.S. population.* Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA-450/3-92-011.

Keenan, R. E., Paustenbach, D. J., Wenning, R. J., and Parsons, A. H. 1991. Pathology reevaluation of the Kociba et al. (1978) bioassay of 2,3,7,8-TCDD: Implications for risk assessment. *J. Toxicol. Environ. Health* 34:279–296.

Kerger, B. D., Leung, H. W., Paustenbach, D. J., Needham, L. L., Patterson, D. G., Jr., Gerthoux, P. M., and Mocarelli, P. 2005a. Age- and concentration dependent TCDD elimination kinetics in Seveso children. *Organohalogen Compounds* 67:1722–1725.

Kerger, B. D., Leung, H. W., Scott, P. K., and Paustenbach, D. J. 2005b. Refinements on the age-dependent half-life model for estimating childhood body burdens of dibenzodioxins and dibenzofurans. *Chemosphere,* in press.

Kerger, B. D., Paustenbach, D. J., and Richter, R. O. 2005c. Unpublished calculations.

Kerkvliet, N. I. 1995. Immunological effects of chlorinated dibenzo-*p*-dioxins. *Environ. Health Perspect.* 103:47–53.

Kimbrough, R. D., Falk, H., Stehr, P., and Fries, G. 1984. Health implications of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) contamination of residential soil. *J. Toxicol. Environ. Health* 14:47–93.

Kociba, R. J., Keyes, D. G., Beyer, J. E., Carreon, R. M., Wade, C. E., Dittenber, D. A., Kalnins, R. P., Frauson, L. E., Park, C. N., Barnard, S. D., Hummel, R. A., and Humiston, C. G. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rats. *Toxicol. Appl. Pharmacol.* 46:279–303.

Kogevinas, M. 2001. Human health effects of dioxins: cancer, reproductive and endocrine system effects. *Hum. Reprod. Update* 7:331–339.

Krablin, R. 1989. [Letter to Jonathan Z. Cannon concerning soil ingestion rates.] Denver, CO: Arco Coal Co., October 13 (as cited in U.S. EPA, 1997a).

Kreuzer, P. E., Csanady, G. A., Baur, C., Kessler, W., Papke, O., Greim, H., and Filser, J. G. 1997. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and congeners in infants. A toxicokinetic model of human lifetime body burden by TCDD with special emphasis on its uptake by nutrition. *Arch. Toxicol.* 71:383–400.

Larsen, J. C., Farland, W., and Winters, D. 2000. Current risk assessment approaches in different countries. *Food Addit. Contam.* 2000:359–369.

Leung, H. W., Kerger, B. D., and Paustenbach, D. J. 2005a. Elimination half-lives of selected polychlorinated dibenzodioxins and dibenzofurans in breast-fed human infants. *J. Toxicol. Environ. Health A.*

Leung, H. W., Kerger, B. D., Paustenbach, D. J., Ryan, J. J., and Masuda, Y. 2005b. Age- and concentrations-dependent clearance kinetics of polychlorinated dibenzofurans in Yusho and Yucheng patients. *Organohalogen Compounds* 67:1726–1729.

Lipsky, D. 1989. Assessment of potential health hazards associated with PCDD and PCDF emissions from a municipal waste combustor. In *The risk assessment of environmental hazards*, eds. D. J. Paustenbach, pp. 631–686. New York: John Wiley and Sons.

Lorber, M. 2001. Indirect exposure assessment at the United States Environmental Protection Agency. *Toxicol. Ind. Health.* 17:145–156.

Lucier, G. W., Rumbaugh, R. C., McCoy, Z., Hass, R., Harvan, D., and Albro, P. 1986. Ingestion of soil contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) alters hepatic enzyme activities in rats. *Fundam. Appl Toxicol.* 6:364–371.

Mably, T. A., Bjerke, D. L., Moore, R. W., Gendron-Fitzpatrick, A., and Peterson, R. E. 1992a. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. 3. Effects on spermatogenesis and reproductive capability. *Toxicol. Appl. Pharmacol.* 114:118–126.

Mably, T. A., Moore, R. W., Goy, R. W., and Peterson, R. E. 1992b. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. *Toxicol. Appl. Pharmacol.* 114:108–117.

Madsen, C., and Larsen, J. C. 1989. Relative toxicity of chlorinated dibenzo-*para*-dioxins, and dibenzofurans measured by thymus and liver-enzyme induction in perinatally dosed rats 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, 1,2,3,7,8-PCDD. *Chemosphere* 18:955–966.

Maronpot, R. R., Montgomery, C. A., Jr., Boorman, G. A., and McConnell, E. E. 1986. National Toxicology Program nomenclature for hepatoproliferative lesions of rats. *Toxicol. Pathol.* 14:263–273.

McConnell, E. E., Lucier, G. W., Rumbaugh, R. C., Albro, P. W., Harvan, D. J., Hass, J. R., and Harris, M. W. 1984. Dioxin in soil: Bioavailability after ingestion by rats and guinea pigs. *Science* 223:1077–1079.

McConnell, E. E., Solleveld, H. A., Swenberg, J. A., and Boorman, G. A. 1988. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. In *Carcinogenicity, The design, analysis, and interpretation of long-term animal studies*, eds. H. C. Grice and J. L. Cimineri, pp. 183–196. New York: ILSI Monographs, Springer Verlag.

Michigan Department of Environmental Quality. 2001. *Part 201 Generic soil direct contact criteria technical support document*. Lansing, MI: Michigan Department of Environmental Quality. http://www.deq.state.mi.us/documents/deq-whm-hwp-excerpt_of_dcc_tsd.pdf.

Ministry for the Environment and Ministry of Health. 1997. *Health and environmental guidelines for selected timber treatment chemicals, New Zealand*. www.mfe.govt.nz/publications.

Ministry of Environment. 2001. *Dioxins*. Council of Ministries and Agencies on Dioxin Policy, Government of Japan. www.env.go.jp/en/topic/dioxin/brochure2003.pdf.

Mocarelli, P., Marocchi, A., Brambilla, P., Gerthoux, P., Young, D. S., and Mantel, N. 1986. Clinical laboratory manifestations of exposure to dioxin in children. A six-year study of the effects of an environmental disaster near Seveso, Italy. *J. Am. Med. Assoc.* 256:2687–2695.

Mocarelli, P., Needham, L. L., Marocchi, A., Patterson, D.G., Brambilla, P., Gerthoux, P. M., Meazza, L., and Carreri, V. 1991. Serum concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and test results from selected residents of Seveso, Italy. *J. Toxicol. Environ. Health* 32:357–366.

Moolgavkar, S. H. 1986. Carcinogenesis modeling: From molecular biology to epidemiology. *Annu. Rev. Public Health* 7:151–169.

Moolgavkar, S. H., and Knudson, A. G., Jr. 1981. Mutation and cancer: a model for human carcinogenesis. *J. Nat. Cancer Inst.* 66:1037–1052.

Moolgavkar, S. H., and Luebeck, G. 1990. Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations. *Risk Anal.* 10:323–341.

Moolgavkar, S. H., Dewanji, A., and Venzon, D. J. 1988. A stochastic two-stage model for cancer risk assessment. I. The hazard function and the probability of tumor. *Risk Anal.* 8:383–392.

Muller, J. F., Hulster, A., Papke, O., Ball, M., and Marschner, H. 1994. Transfer of PCDD/PCDF from contaminated soils into carrots, lettuce and peas. *Chemosphere* 29(9-11):2175–2181.

Murray, D. M., and Burmaster, D. E. 1992. Estimated distributions for total body surface area of men and women in the United States. *J. Expos. Anal. Environ. Epidemiol.* 2:451–461.

Murray, F. J., Smith, F. A., Nitschke, K. D., Humiston, C. G., Kociba, R. J., and Schwetz, B. A. 1979. Three generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the diet. *Toxicol. Appl. Pharmacol.* 50:241–251.

National Toxicology Program. 1982. *Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (CAS No. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (gavage study)*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 209. NIH Publication No. 82-1765.

National Academy of Sciences. 1983. *Risk assessment in the federal government: Managing the process*. Washington, DC: National Academy of Sciences.

National Academy of Sciences. 1994. *Science and judgment in risk assessment*. Washington, DC: National Academy of Sciences.

National Academy of Sciences. 1999. *Arsenic in drinking water*. Washington, DC: National Academy of Sciences.

National Toxicology Program. 2001. *Addendum to the ninth report on carcinogens*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. http://ehp.niehs.nih.gov/roc/ninth/known/tcdd.pdf.

National Toxicology Program. 2004. *Draft NTP technical report on the toxicology and carcinogenesis studies of 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (TCDD) (CAS No. 1746-01-6) in female Harlan Sprague-Dawley rats (Gavage study)*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 521. NIH Publication No. 04-4455.

Neubert, R., Golor, G., Stahlmann, R., Helge, H., and Neubert, D. 1992. Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune system. 4. Effects of multiple-dose treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on peripheral lymphocyte subpopulations of a non-human primate (*Callithrix jacchus*). *Arch. Toxicol.* 66:250–259.

Nichols, A. L., and Zeckhauser, R. J. 1988. The perils of prudence: How conservative risk assessments distort regulation. *Regul. Toxicol. Pharmacol.* 8:61–75.

Norback, D. H., Engblom, J. F., and Allen, J. R. 1975. Tissue distribution and excretion of octachlorodibenzo-*para*-dioxin in the rat. *Toxicol. Appl. Pharmacol.* 32:330–338.

OEHHA Office of Environmental Health Hazard Assessment. 2004. Article 7. No significant risk levels. In Proposition 65 - TITLE 22, Division 2, Part 2, Subdivision 1, Chapter 3, California Code of Regulations, eds.

Ohsako, S., Miyabara, Y., Nishimura, N., Kurosawa, S., Sakaue, M., Ishimura, R., Sato, M., Takeda, K., Aoki, Y., Sone, H., Tohyama, C., and Yonemoto, J. 2001. Maternal exposure to a low dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) suppressed the development of reproductive organs of male rats: Dose-dependent increase of mRNA levels of 5alpha-reductase type 2 in contrast to decrease of androgen receptor in the pubertal ventral prostate. *Toxicol. Sci.* 60:132–143.

Ontario Ministry of Environment. 1985. *Polychlorinated dibenzo*-p-*dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)*. Scientific criteria document for standard development No. 4–84. Intergovernmental Relations and Hazardous Contaminants Coordination Branch, Ontario, Canada, September.

Ostby, J., Price, M., Huey, O., Hurst, C., Birnbaum, L., and Gray, L. J. 1999. Developmental and reproductive effects of low-dose, steady-state maternal 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) administration. *Toxicol. Sci.* 48:147.

Ott, M. G., and Zober, A. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. *Occup. Environ. Med.* 53:606–612.

Palisade. 2005. *@Risk software*. Newfield, NY: Palisade Corporation.

Pathology Working Group. 1990a. *Hepatotoxicity in female Sprague Dawley rats treated with 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (TCDD)*. Submitted to R. A. Michaels, Chairperson, Maine Scientific Advisory Panel. Maine: PATHCO, Inc.

Pathology Working Group. 1990b. *2,3,7,8-Tetrachlorodibenzo*-p-*dioxin chronic toxicity/carcinogenicity study in Sprague Dawley rats*. Submitted to R. A. Michaels Chairperson, Maine Scientific Advisory Panel. Maine: PATHCO, Inc.

Paustenbach, D. J. 1987. Assessing the potential environmental and human health risks of contaminated soil. *Comm. Toxicol.* 1:185–220.

Paustenbach, D. J. 1989. Important recent advances in the practice of health risk assessment: implications for the 1990s. *Regul. Toxicol. Pharmacol.* 10:204–243.

Paustenbach, D. J. 2000. The practice of exposure assessment: A state-of-the-art review. *J. Toxicol. Environ. Health B* 3:179–291.

Paustenbach, D. J. 2002a. *Human and ecological risk assessment: Theory and practice*. New York: John Wiley and Sons.

Paustenbach, D. J. 2002b. The U.S. EPA Science Advisory Board evaluation (2001) of the EPA dioxin reassessment. *Regul. Toxicol. Pharmacol.* 36:211–219.

Paustenbach, D. J., Shu, H. P., and Murray, F. J. 1986. A critical examination of assumptions used in risk assessments of dioxin contaminated soil. *Regul. Toxicol. Pharmacol.* 6:284–307.

Paustenbach, D. J., Layard, M. W., Wenning, R. J., and Keenan, R. E. 1991a. Risk assessment of 2,3,7,8-TCDD using a biologically based cancer model: A reevaluation of the Kociba et al. bioassay using 1978 and 1990 histopathology criteria. *J. Toxicol. Environ. Health* 34:11–26.

Paustenbach, D. J., Sarlos, T. T., Lau, V., Finley, B. L., Jeffrey, D. A., and Ungs, M. J. 1991b. The potential inhalation hazard posed by dioxin contaminated soil. *J. Air Waste Manage. Assoc.* 41:1334–1340.

Paustenbach, D. J., Jernigan, J. D., Bass, R., Kalmes, R., and Scott, P. 1992a. A proposed approach to regulating contaminated soil: Identify safe concentrations for seven of the most frequently encountered exposure scenarios. *Regul. Toxicol. Pharmacol.* 16:21–56.

Paustenbach, D. J., Wenning, R. J., Lau, V., Harrington, N. W., Rennix, D. K., and Parsons, A. H. 1992b. Recent developments on the hazards posed by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in soil: Implications for setting risk-based cleanup levels at residential and industrial sites. *J. Toxicol. Environ. Health* 36:103–149.

Paustenbach, D. J., Leung, H. W., Scott, P. K., and Kerger, B. D. 2004. An approach to calculating childhood body burdens of dibenzodioxins and dibenzofurans which accounts for age-dependent biological half-lives. *Organohalogen Compounds* 66:2714–2721.

Pohl, H., Hicks, H. E., Jones, D., Hansen, H., and De Rosa, C. T. 2002. Public health perspectives on dioxin risks: Two decades of evaluations. *Hum. Ecol. Risk Assess.* 8:233–250.

Poiger, H., and Schlatter, C. 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. *Food Cosmet. Toxicol.* 18:477–481.

Poiger, H., and Schlatter, C. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. *Chemosphere* 15:1489–1494.

Poland, A. P., Smith, D., Metter, G., and Possick, P. 1971. A health survey of workers in a 2,4,-D and 2,4,5-T plan with special attention to chloracne, porphyria cutanea tarda, and psychological parameters. *Arch. Environ. Health.* 22:316–327.

Popp, J. A., Crouch, E., and McConnell, E. E. 2000. A weight-of-evidence analysis of the cancer dose-response characteristics of 2,3,7,8-tetrachloroddibenzodioxin (TCDD). *Toxicol. Sci*. (Advanced Access published November 2, 2005).

Portier, C. Risk ranges for various endpoints following exposure to 2,3,7,8-TCDD. *Food Addit. Contam.* 17:335–346.

Reggiani, G. 1978. Medical problems raised by the TCDD contamination in Seveso, Italy. *Arch. Toxicol.* 40:161–188.

Renwick, A. 2004. *Recent risk assessments of dioxins*. Plenary lecture at the 24th International Symposium on Halogenated Environmental Organic Pollutants and POPs, Berlin, Germany, September, 8.

Richter, R. O., Kerger, B. D., Leung, H.-W., and Paustenbach, D. J. 2006. Implications of age-dependent half lives of dioxins on assessment of breast milk dose and body burden. *Society of Toxicology Annual Meeting*. (Abstract Accepted).

Rier, S. E., Martin, D. C., Bowman, R. E., Dmowski, W. P., and Becker, J. L. 1993. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Fundam. Appl. Toxicol.* 21:433–441.

Rose, J. Q., Ramsey, J. C., Wentzler, T. H., Hummel, R. A., and Gehring, P. J. 1976. The fate of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin following single and repeated oral doses to the rat. *Toxicol. Appl. Pharmacol.* 36:209–226.

Roy, T. A., Yang, J. J., Krueger, A. J., and Mackerer, C. R. 1990. Percutaneous absorption of neat 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and TCDD sorbed on soils. *Toxicology* 10:308–321.

Ruby, M. V., Fehling, K. A., Paustenbach, D. J., Landenberger, B. D., and Holsapple, M. P. 2002. Oral bioaccessibility of dioxins/furans at low concentrations (50–350 ppt toxicity equivalent) in soil. *Environ. Sci. Technol.* 36:4905–4911.

Safe, S. 1997. Limitations of the toxic equivalency factor approach for risk assessment of TCDD and related compounds. *Teratogen. Carcinogen. Mutagen.* 17:285–304.

Safe, S. H. 1998. Hazard and risk assessment of chemical mixtures using the toxic equivalency factor approach. *Environ. Health Perspect.* 106:1051–1058.

Safe, S. 2001. Molecular biology of the Ah receptor and its role in carcinogenesis. *Toxicol. Lett.* 120:1–7.

Schantz, S. L., Ferguson, S. A., and Bowman, R. E. 1992. Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on behavior of monkeys in peer groups. *Neurotoxicol. Teratol.* 14:433–446.

Schaum, J. 1983. *Risk analysis of TCDD contaminated soil.* Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC.

Schlatter, C., and Poiger, H. 1985. *Assessment of contamination with 2,3,7,8-TCDD.* Zurich: Swiss Institute of Toxicology, University of Zurich.

Sheehan, P. J., Meyer, D. M., Sauer, M. M., and Paustenbach, D. J. 1991. Assessment of the human health risks posed by exposure to chromium-contaminated soils. *J. Toxicol. Environ. Health* 32:161–201.

Sheppard, S. C. 1995. Parameter values to model the soil ingestion pathway. *Environmental Monitoring and Assessment* 34:27–44.

Shlyakhter, A., Goodman, G., and Wilson, R. 1992. Monte Carlo simulation of rodent carcinogenicity bioassays. *Risk Anal.* 12:73–82.

Shu, H. P., Paustenbach, D. J., and Murray, F. J. 1987. A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Regul. Toxicol. Pharmacol.* 7:57–88.

Shu, H., Paustenbach, D., Murray, F. J., Marple, L., Brunck, B., Dei Rossi, D., and Teitelbaum, P. 1988. Bioavailability of soil-bound TCDD: Oral bioavailability in the rat. *Fundam. Appl. Toxicol.* 10:648–654.

Sielken, R. L., Jr. 1987. Quantitative cancer risk assessments for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *Food Chem. Toxicol.* 25:257–267.

Sielken, R. L., Jr., and Stevenson, D. E. 1998. Some implications for quantitative risk assessment if hormesis exists. *Hum. Exp. Toxicol.* 17:259–262.

Sielken, R. L., Jr., Bretzlaff, R. S., and Stevenson, D. E. 1995. Challenges to default assumptions stimulate comprehensive realism as a new tier in quantitative cancer risk assessment. *Regul. Toxicol. Pharmacol.* 21:270–280.

Smith, A. E., Ryan, P. B., and Evans, J. S. 1992. The effect of neglecting correlations when propagating uncertainty and estimating the population distribution of risk. *Risk Anal.* 12:467–474.

Smith, A. H., and Lopipero, P. 2001. Invited commentary: How do the Seveso findings affect conclusions concerning TCDD as a human carcinogen? *Am. J. Epidemiol.* 153:1045–1047. discussion 1048–1049.

Squire, R. A. 1980. *Pathologic evaluations of selected tissues from the Dow Chemical TCDD and 2,4,5-T rat studies.* Document submitted to Carcinogen Assessment Group, U.S. Environmental Protection Agency, Washington, DC.

Squire, R. A., and Levitt, M. H. 1975. Report of a workshop on classification of specific hepatocellular lesions in rats. *Cancer Res.* 35:3214–3223.

Stanek, E. J., and Calabrese, E. J. 1991. A guide to interpreting soil ingestion studies. I. Development of a model to estimate the soil ingestion detection level of soil ingestion studies. *Regul. Toxicol. Pharmacol.* 13:263–277.

Stanek, E. J., and Calabrese, E. J. 1995. Daily estimates of soil ingestion in children. *Environ. Health Perspect.* 103:276–285.

Stanek, E. J., and Calabrese, E. J. 2000. Daily soil ingestion estimates for children at a Superfund site. *Risk Anal.* 20:627–635.

Stanek, E. J., Calabrese, E. J., Barnes, R., and Pekow, P. 1997. Soil ingestion in adults—Results of a second pilot study. *Ecotoxicol. Environ. Safety* 36:249–257.

Stanek, E. J., Well, A., and Ockene, I. 1999. Why not routinely use best linear unbiased predictors (BLUPs) as estimates of cholesterol, percent fat from kcal and physical activity? *Stat. Med.* 18:2943–2959.

Stanek, E. J., Calabrese, E. J., and Zorn, M. 2001. Soil ingestion distributions for monte carlo risk assessment in children. *Hum. Ecol. Risk Assess.* 7:357–368.

Starr, T. B. 2001. Significant shortcomings of the U.S. Environmental Protection Agency's latest draft risk characterization for dioxin-like compounds. *Toxicol. Sci.* 64:7–13.

Starr, T. B. 2003. Significant issues raised by meta-analyses of cancer mortality and dioxin exposure. *Environ. Health Perspect.* 111:1443–1447.

Starr, T. B., Greenlee, W. F., Neal, R. A., Poland, A., and Sutter, T. R. 1999. The trouble with TEFs. *Environ. Health Perspect.* 107:A492–A493.

Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M., and Chang, L. I. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *JNCI* 91:779–786.

Steenland, K., Deddens, J., and Piacitelli, L. 2001. Risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) based on an epidemiologic study. *Am. J. Epidemiol.* 154:451–458.

Susten, A. 2004. Personal communication to D. J. Paustenbach. Dr. Susten is a retired scientist formally employed by ATSDR and CDC. The cited statements are based on observations and opinions of Dr. Susten and do not necessarily reflect the opinions or policies of ATSDR or CDC.

Sweeney, M. H., and Mocarelli, P. 2000. Human health effects after exposure to 2,3,7,8-TCDD. *Food Addit. Contam.* 17:303–316.

Travis, C. C., Richter, S. A., Crouch, E. A. C., Wilson, R., and Klema, E. D. 1987. Cancer risk management: A review of 132 federal regulatory decisions. *Environ. Sci. Technol.* 21:415–420.

Tukey, J. W. 1977. *Exploratory data analysis.* Boston: Addison-Wesley.

Umbreit, T. H., Hesse, E. J., and Gallo, M. A. 1986. Bioavailability of dioxin in soil from a 2,4,5-T manufacturing site. *Science* 232:497–499.

United Kingdom. 1989. *Dioxins in the environment*. Report of an interdepartmental working group on polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Pollution Paper no. 27. Central Directorate of Environmental Protection.

University of Michigan. 2005. *University of Michigan dioxin exposure study*. Ann Arbor, MI. Description of the study including protocol can be found on www.umich.edu.

U.S. Environmental Protection Agency. 1985. *Health assessment document for polychlorinated dibenzo*-p-*dioxins*. Washington, DC: U.S. EPA. Final Report. EPA/800–8–84/01 4F. September.

U.S. Environmental Protection Agency. 1986. *Superfund public health evaluation manual; OSWER Directive 9285.4-1.* Washington, DC: U.S. EPA. USEPA/540/1-86/060.

U.S. Environmental Protection Agency. 1989a. Integrated Risk Information System (IRIS) on-line database entry for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. January 1.

U.S. Environmental Protection Agency. 1989b. *Risk assessment guidance for Superfund. Volume 1, Human health evaluation manual. Part A.* Washington, DC: U.S. EPA. USEPA/540/1-89/002.

U.S. Environmental Protection Agency. 1990. National oil and hazardous substances pollution contingency plan. *Fed. Reg.* 55:866.

U.S. Environmental Protection Agency. 1991. *Human health evaluation manual, supplemental guidance: Standard default exposure factors*. Washington, DC: Toxics Integration Branch, U.S. EPA.

U.S. Environmental Protection Agency. 1992. *Dermal exposure assessment: Principles and applications*. Washington, DC: U.S. EPA. EPA/600/8-91/011B.

U.S. Environmental Protection Agency. 1995a. *Great Lakes water quality initiative criteria documents for the protection of human health.* Washington, DC: U.S. EPA. USEPA-820B-95-006.

U.S. Environmental Protection Agency. 1995b. *Guidance for risk characterization.* Memo from Carol M. Browner, U.S. EPA Assistant Administrator. Washington, DC: U.S. EPA Science Policy Council.

U.S. Environmental Protection Agency. 1997a. *Exposure factors handbook (EFH)*, vols. I, II and III. Washington, DC. USEPA/600/P-95/002Fa, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12464.

U.S. Environmental Protection Agency. 1997b. *Guiding principles for Monte Carlo analysis*. Risk Assessment Forum, Washington, DC. USEPA/630/R-97/001, http://www.epa.gov/ncea/raf/montecar.pdf.

U.S. Environmental Protection Agency. 1997c. Memorandum from Deputy Administrator Fred Hansen on the use of probabilistic techniques (including monte carlo analysis in risk assessment and guiding principles for Monte Carlo analysis). Washington, DC.

U.S. Environmental Protection Agency. 1998. *Human health risk assessment protocol for hazardous waste combustion facilities*, vols. I, II, and III. Peer reviewed draft. Washington, DC. USEPA/530-D-98-001A, http://www.epa.gov/Arkansas/6pd/rcra_c/protocol/metarisk.htm.

U.S. Environmental Protection Agency. 2000a. *Child-specific exposure factors handbook*. Washington, DC. NCEA-W-0853. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?PrintVersion=True&deid=17880.

U.S. Environmental Protection Agency. 2000b. *Draft exposure and human health risk assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds*, parts I, II, and III. Washington, DC. USEPA/600/P-00/001Bg, http://cfpub.epa.gov/ncea/cfm/part1and2.cfm?ActType=default.

U.S. Environmental Protection Agency. 2001a. *Risk assessment guidance for Superfund*, vol. I, *Human health evaluation manual* (part E, supplemental guidance for dermal risk assessment). Washington, DC. USEPA/540/R/99/005, http://www.epa.gov/oswer/riskassessment/ragse/pdf/introduction.pdf.

U.S. Environmental Protection Agency. 2001b. *Risk assessment guidance for Superfund*, vol. III (part A, process for conducting probabilistic risk assessment). Washington, DC. http://www.epa.gov/oswer/riskassessment/ragsa/index.htm.

U.S. Environmental Protection Agency. 2003. *Draft exposure and human health risk assessment of 2,3,7,8-tetrachlorodibenzo*-p-*dioxin (TCDD) and related compounds*, parts I, II and III. Washington, DC. http://www.epa.gov/ncea/pdfs/dioxin/nas-review/.

U.S. Environmental Protection Agency. 2004. *An examination of USEPA risk assessment principles and practices.* Washington, DC: U.S. EPA. EPA/600/8-91/011B.

U.S. Environmental Protection Agency. Science Advisory Board. 2001. *Dioxin reassessment. An SAB review of the Office of Research and Development's reassessment of dioxin*. Washington, DC. USEPA-SAB-EC-01-006, http://www.epa.gov/sab/pdf/ec01006.pdf. May 31.

U.S. EPA. 1991. Percutaneous absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3,3'4,4'-tetrachlorobiphenyl (TCB) applied in soil. Office of Health and Environmental Assessment. Available from Exposure Assessment Group, Washington, DC. OHEA-E-453.

U.S. Food and Drug Administration. 1983. Statement by Sanford A. Miller, Ph.D., Director, Bureau of Foods, Food and Drug Administration, before the Subcommittee on Natural Resources, Agriculture, Research and Environment, Committee on Science and Technology, U.S. House of Representatives, June 30.

Van Birgelen, A. P., Van der Kolk, J., Fase, K. M., Bol, I., Poiger, H., Brouwer, A., and Van den Berg, M. 1995. Subchronic dose-response study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in female Sprague-Dawley rats. *Toxicol. Appl. Pharmacol.* 132:1–13.

Van den Berg, M., Birnbaum, L., Bosveld, A. T., Brunstrom, B., Cook, P., Feeley, M., Giesy, J. P., Hanberg, A., Hasegawa, R., Kennedy, S. W., Kubiak, T., Larsen, J. C., van Leeuwen, F. X., Liem, A. K., Nolt, C., Peterson, R. E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F., and Zacharewski, T. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.* 106:775–792.

Van den Berg, M., DeVroom, M., van Greevenbroek, M., and Olie, K. 1985. Bioavailability of PCDDs and PCDFs absorbed on fly ash in rat, guinea pig and Syrian golden hamster. *Chemosphere* 14:865–869.

Van den Berg, M., Heeremans, C., Veenhoven, E., and Olie, K. 1987. Transfer of polychlorinated dibenzo-p-dioxins and dibenzofurans to fetal and neonatal rats. *T. Fundam. Appl. Toxicol.* 9:635–644.

Van den Berg, M., Ollie, K., and Hutzinger, O. 1983. Uptake and selective retention in rats of orally administered chlorinated dioxins and dibenzofurans from fly-ash and fly-ash extract. *Chemosphere* 12:537–544.

van Wijnen, J. H., Clausing, P., and Brunekreef, B. 1990. Estimated soil ingestion by children. *Environ. Res.* 51:147–162.

Viluksela, M., Stahl, B. U., and Rozman, K. K. 1994. Subchronic (13-week) toxicity of heptachlorodibenzo-*p*-dioxin in male Sprague-Dawley rats. *Chemosphere* 29:2381–2393.

Walker, N. J., Crockett, P. W., Nyska, A., Brix, A. E., Jokinen, M. P., Sells, D. M., Hailey, J. R., Easterling, M., Haseman, J. K., Yin, M., Wyde, M. E., Bucher, J. R., and Portier, C. J. 2005. Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds.". *Environ. Health Perspect* 113:43–48.

Williams, P. R., and Paustenbach, D. J. 2002. Risk characterization: Principles and practice. *J. Toxicol. Environ. Health B* 5:337–406.

Wipf, H. K., Homberger, E., Neimer, N., Ranalder, U. B., Vetter, W., and Vuilleumier, J. P. 1982. TCDD-levels in soil and plant samples from the Seveso area. In *Chlorinated dioxins and related compounds: Impact on the environment*, eds. R. W. F. O. Hutzinger, E. Merian, and F. Pocchiari, pp. 115–126. New York: Pergamon Press.

World Health Organization. 1991. *Consultation on tolerable daily intake from food of PCDDs and PCDFs*. Copenhagen, Denmark. Summary Report. Bilthoven, Netherlands. EUR/IPC/PCS 030(S). December 4–7, 1990.

World Health Organization. 2000. Assessment of health risk of dioxins: Re-evaluation of the tolerable daily intake (TDI). *Food Addit. Contam.* 17:233–369.

World Health Organization. 2001. Joint FAO/WHO Expert Committee on Food Additives (JECFA), fifty-seventh meeting, Rome, 5–14 June. Summary and conclusions. Food and Agriculture Organization of the United Nations. http:/www.who.int/ipcs/food/jecfa/summaries/en/summary_57.pdf.

World Health Organization. 2005. *Announcement of project for the re-evaluation of human and mammalian toxic equivalency factors (TEFs) of dioxins and dioxin-like compounds and request for information*. http://www.who.int/ipcs/assessment/tef_review/en/.

Yoshizawa, K., Walker, N. J., Jokinen, M. P., Brix, A. E., Sells, D. M., Marsh, T., Wyde, M. E., Orzech, D., Haseman, J. K., and Nyska, A. 2005. Gingival carcinogenicity in female Harlan Sprague-Dawley rats following two-year oral treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and dioxin-like compounds. *Toxicol. Sci.* 83:64–77.