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Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Dioxin-Like Compounds

Office of the Science Advisor
Risk Assessment Forum

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Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

NOTICE

This report has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

This document describes the U.S. Environmental Protection Agency's (EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing dioxin-like compounds (DLCs). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and DLCs are structurally and toxicologically related halogenated aromatic hydrocarbons. The EPA recommends that the toxicity equivalence factor (TEF) methodology, a component mixture method, be used to evaluate human health risks posed by these mixtures, using TCDD as the index chemical. The EPA recommends the use of the consensus TEF values for TCDD and the DLCs published in 2005 by the World Health Organization. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. The EPA recommends these TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by the DLCs including cancer and noncancer effects. Using information that summarizes the range of relative toxicities of the DLCs, the EPA recommends that, for major risk assessments as determined by U.S. EPA Program Offices or Regions, the conduct of a sensitivity analysis be considered to illustrate the impact the TEFs have on the toxicity equivalence (TEQ) value. The EPA will update all of these recommendations in the future based on the evaluation of new toxicity data for the DLCs, updates to available relative potency (ReP) data, including statistical summaries of RePs for individual DLCs, and the results of new consensus processes undertaken to update the TEF approach.

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LIST OF ABBREVIATIONS

AhR	aryl hydrocarbon receptor
DLC	dioxin-like compound
ECEH	European Centre for Environmental Health
ED_{50}	effective dose that causes an effect in 50% of the test units
IPCS	International Programme on Chemical Safety
NAS	National Academy of Science
ReP	relative potency or relative effect potency
ReP_{1997}	World Health Organization ReP database developed in 1997
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	toxicity equivalence factor
TEQ	toxicity equivalence
EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

LIST OF ABBREVIATIONS OF DIOXINS AND DIOXIN-LIKE COMPOUNDS

Polychlorinated biphenyls:

TCB	tetrachlorinated biphenyl
PeCB	pentachlorinated biphenyl
HxCB	hexachlorinated biphenyl
HpCB	heptachlorinated biphenyl
OCB	octachlorinated biphenyl
PCB	polychlorinated biphenyl

Polychlorinated dibenzo-p-dioxins:

TCDD	tetrachlorinated dibenzo-*p*-dioxin
PeCDD	pentachlorinated dibenzo-*p*-dioxin
HxCDD	hexachlorinated dibenzo-*p*-dioxin
HpCDD	heptachlorinated dibenzo-*p*-dioxin
OCDD	octachlorinated dibenzo-*p*-dioxin
PCDD	polychlorinated dibenzo-*p*-dioxin

Polychlorinated dibenzofurans:

TCDF	tetrachlorinated dibenzofuran
PeCDF	pentachlorinated dibenzofuran
HxCDF	hexachlorinated dibenzofuran
HpCDF	heptachlorinated dibenzofuran
OCDF	octachlorinated dibenzofuran
PCDF	polychlorinated dibenzofuran

KEY TERMS

Dioxin-like: A description used for compounds that have chemical structures, physico-chemical properties, and toxic responses similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. Certain members of the dioxin, furan, and polychlorinated biphenyl (PCB) family are termed "dioxin-like" in this document and are assigned toxic equivalence factor (TEF) values.

Index Chemical: The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical must have a clearly defined dose-response relationship. For dioxin like compounds (DLCs), TCDD is typically specified as the index chemical. (In some studies used to develop RePs, PCB_{126} has been used as the index chemical.)

Relative Potency (ReP): The ratio of the potency of a compound to the standard toxicant in that specific study; a concept similar to toxic equivalence but based on a single study, species, or matrix, etc., and not integrated with other RePs to obtain a general TEF.

Toxic Equivalence Factors (TEFs): TEFs are consensus estimates of compound-specific toxicity/potency relative to the toxicity/potency of an index chemical. TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data.

Toxic Equivalence (TEQ): TEQ is the product of the concentration of an individual DLC in an environmental mixture and its corresponding TCDD TEF for that compound.

PREFACE

This document updates the U.S. Environmental Protection Agency's (EPA's) approach for evaluating the human health risks from exposures to environmental media containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs). It is intended for guidance only. It provides guidance to EPA Regional and Program Offices. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no binding effect on EPA or any regulated entity. Rather, it represents a statement of current policy. The EPA's National Center for Environmental Assessment developed the initial draft of this document, which was then reviewed and completed by a Technical Panel under the auspices of EPA's Risk Assessment Forum. EPA made the document available for public comment during a 30 day public comment period in September 2009, and an expert peer-review panel discussed the document in a teleconference open to the public on October 22, 2009. The public comments received by EPA were provided to the peer-review panel members prior to the October 2009 teleconference for their consideration in making comments and recommendations to EPA. The peer-review report, and EPA response to comments, is available at http://www.epa.gov/raf/hhtefguidance/index.htm.

The Risk Assessment Forum was established to promote scientific consensus within EPA on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate risk assessment guidance. To accomplish this, the Risk Assessment Forum assembles experts from throughout EPA in a formal process to study and report on these issues from an Agency-wide perspective.

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INTRODUCTION

This document describes the U.S. Environmental Protection Agency's (EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs). TCDD and DLCs, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs), are structurally and toxicologically related halogenated dicyclic aromatic hydrocarbons.[1]

EPA's chemical mixtures guidelines and guidance documents (U.S. EPA, 1986, 2000) call for the use of whole mixture data or data on a sufficiently similar mixture as preferred risk assessment methods. However, when data are not sufficient to apply these methods, the EPA also recommends component-based approaches. In such situations, the EPA has recommended use of the Toxicity Equivalence Factor (TEF) Methodology and the World Health Organization's (WHO's) TEFs to evaluate the risks associated with exposure to mixtures of TCDD and DLCs for human health (U.S. EPA, 1987, 1989, 2003) and ecological risk assessments (U.S. EPA, 2008). The WHO has used a process based on consensus judgment of scientific expert panels to develop TEFs for mammals, birds, and fish and has re-evaluated them on a schedule of approximately every 5 years (Ahlborg et al., 1994; van den Berg et al., 1998, 2006; also see WHO's Web site for the dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/). After evaluating the empirical data on TCDD and some DLCs, WHO reconfirmed that the combined effects of these compounds generally are consistent with dose additivity, a key underlying assumption of the TEF methodology (van den Berg et al., 2006). In this document, the EPA is updating its human health approach by adopting the mammalian TEFs for DLCs recommended in the WHO's 2005 reevaluation of TEFs for human exposures to DLCs (van den Berg et al., 2006). EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs.

[1]For further information on the chemical structures of these compounds, see U.S. EPA (2003, 2008).

THE TEF METHODOLOGY

This section briefly describes the TEF methodology, which is based on the concept of dose addition. Application of this methodology in human health risk assessment has been described and reaffirmed for use by the Agency in EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000). Under dose addition, the toxicokinetics and the toxicodynamics of all components are assumed to be similar and the dose-response curves of the components of a mixture are assumed to be similarly shaped.[2] Following these assumptions, the combined toxicity of the individual components can be estimated using the sum of their doses, which are scaled for potency relative to that of another component of the mixture for which adequate dose-response information is available (U.S. EPA, 2000).

In practice, the scaling factor for each DLC is typically based on a comparison of its toxic potency to that of a designated index chemical. For DLCs, TCDD is typically specified as the index chemical. However, the WHO 2005 (van den Berg et al., 2006) panel also used PCB_{126} as an index chemical for some DLCs in some studies used to develop relative potency estimates; the panel invoked transitivity, that is, by quantifying both the toxicity of a DLC relative to PCB_{126} and PCB_{126} to TCDD, the toxicity of the DLC relative to TCDD was estimated (RePs; Haws et al., 2006).[3] The index chemical is well-studied toxicologically and must have a dose-response function to apply the methodology to an environmental mixture. The

[2] The TEF methodology has traditionally required that the dose response curves of the DLCs be parallel. In recent years, EPA's guidance documents on chemical mixtures risk assessment have moved away from the strict dose-response requirement of parallelism because of the variability inherent in showing such a phenomenon when dose-response data across mixture components are typically from different labs, different experimental designs or dose levels, and various strains, species, and genders of experimental animals. Further, it can be difficult to evaluate the shapes of dose response curves from experimental studies in the low dose region of interest in risk assessment. For the EPA's relative potency factor method, which is based on dose-addition, only similarly shaped dose response curves are required (satisfied, for example, by modeling the mixture components using the same dose-response functional form, or grouping chemicals by common slope parameters or by a common maximum effect) and may be limited to a range of exposure conditions, including dose level, frequency and route (U.S. EPA, 2000, 2002).

[3] For some compounds in some toxicity studies, the WHO panel compared the toxicity of DLCs to that of PCB_{126} during their development of estimates of RePs (Haws et al., 2006). When developing RePs based on comparing effects of DLCs to those of PCB_{126}, the WHO panel invoked transitivity; that is, by quantifying both the toxicity of a DLC relative to PCB_{126} and PCB_{126} to TCDD, one could estimate the toxicity of the DLC relative to TCDD. Given the TEF for PCB_{126} was 0.1, WHO (2005) multiplied the PCB_{126}-based ReP by 0.1. Based on Hawes et al. (2006), a total 114 RePs were developed for the mono-ortho PCBs in the TEF database. PCB126 served as the index chemical for 29 (25.4%) of these. For the nonortho-PCBs in the same database, if PCB126 is excluded from the nonortho PCBs in the TEF database, then PCB126 served as the index chemical for 18 of 91 (20%) of the RePs.

toxicological data considered for these comparisons of toxic potency are from both in vitro and in vivo studies as well as structure-activity relationships and are based on the following classes of measure: biochemical changes, toxicity, and carcinogenicity. A comparative measure from an individual toxicity assay is termed an estimate of relative potency (ReP).[4] Based on the RePs that may be estimated from multiple toxicological assays, each individual PCDD, PCDF, and PCB is assigned a single scaling factor termed the TEF. By definition, the TEF for TCDD is 1.0; when PCB_{126} serves as an index chemical the value of its TEF is 0.1 (U.S. EPA, 1989, 2000, 2003, 2008; van den Berg et al., 1998, 2006).

To apply TEFs to an environmental mixture of DLCs, each individual compound's exposure concentration is multiplied by its specific TEF, yielding the individual PCDD, PCDF, or PCB dose that is equivalent to a dose of the index chemical. These index chemical equivalent doses are then summed. To estimate risk associated with the mixture, the dose-response function for the index chemical is evaluated at this sum, which is an estimate of the total index chemical equivalent dose for the mixture components being considered.

Equation 1 is the formula for calculating exposure concentration for *n* DLCs in a mixture in TCDD toxic equivalence (TEQ). Exposure to the i^{th} individual PCDD, PCDF, or PCB compound is expressed in terms of an equivalent exposure of TCDD by computing the product of the concentration of the individual compound (C_i) and its assigned TEF_i. TEQ is then calculated by summing these products across the *n* DLC present in the mixture. For human health risk assessment, the TEQ may be evaluated using TCDD dose-response data and used to assess the risk posed by exposures to mixtures of TCDD and DLCs.

$$TEQ = \sum_{i=1}^{n} (C_i \times TEF_i) \qquad \text{(Eq. 1)}$$

[4]The term "relative effect potency" (ReP) also is used at times. This term is distinguished from the 'relative potency factors' (RPF) method, which is a general dose additive method described in U.S. EPA (2000). van den Berg et al. (2006) evaluated RePs based on biochemical and toxicological endpoints (also see related discussion in Haws et al., 2006).

BACKGROUND

There is a long history of the development of TEFs and the TEF methodology, dating back to the 1980s (see Table 1 for details). Early EPA documents recommended the use of the TEF approach for specific PCDDs and PCDFs for environmental risk assessment (U.S. EPA, 1987, 1989). The PCBs that displayed dioxin-like activity were added to the available TEFs for DLCs in 1994 (Ahlborg et al., 1994). Then, in 1997, consensus TEFs were assigned to the DLCs during a meeting held by the WHO (van den Berg et al., 1998); in 2003, EPA recommended the use of the 1997 WHO mammalian TEFs for human health risk assessment (U.S. EPA, 2003).

Besides the inherent assumption of dose additivity that underpins the TEF approach (i.e., the toxicokinetics and the toxicodynamics of all components are assumed to be similar and the dose-response curves of the components of a mixture are assumed to be similarly shaped), limitations in the available toxicity data for the DLCs resulted in a number of additional assumptions that were associated with this approach as implemented. These assumptions included:

- the Ah receptor mediates most if not all of the biologic and toxic effects of TCDD and the DLCs;
- the applicability of extrapolations from short-term bioassays to long-term health effects;
- similarities between interspecies kinetics and potency;
- appropriateness of high-dose to low-dose extrapolations; and
- the constancy of TEF relationships for different exposure routes, health endpoints, and dose levels

(U.S. EPA, 1989, 2000, 2003; see also Birnbaum and DeVito [1995] and Birnbaum [1999]).

Toxic effects of a DLC induced through mechanisms other than the Ah receptor are not accounted for in this method. Similarly, the TEF methodology does not account for the interactions of TCDD and DLCs with each other or with other chemicals to which individuals are exposed. (U.S. EPA [2000] defines the term “interaction” to refer to effects resulting from a mixture of chemicals that are greater than or less than those anticipated to occur as a

Table 1. Background and history of TEFs for risk assessment of DLCs

Publication	Description of historical context
OME, 1984	First to conclude that PCDDs and PCDFs share a common mechanism of action (activation of the AhR) and that a toxic equivalency approach should be used to compare equivalent group concentrations to TCDD.
U.S. EPA, 1986	EPA Guidelines for chemical mixtures risk assessment endorse EPA use of dose addition approaches for chemicals with the same mode of action.
Eadon et al., 1986	First to describe a TEF-like approach.
U.S. EPA, 1987	Recommends EPA use a TEF approach, applying it to specific PCDDs and PCDFs instead of to equivalent group concentrations.
NATO, 1988	Concludes TEF approach is the best available interim approach for PCDD/PCDF risk assessment. Presents an international TEF scheme.
U.S. EPA, 1989	EPA adopts the international TEF scheme developed by NATO (1988) for use in developing interim estimates of risk from exposure to PCDDs and PCDFs.
Barnes et al., 1991	EPA holds workshop. Guiding criteria for TEF approaches are developed. Concludes that PCBs displaying dioxin-like activity meet the criteria for inclusion in the TEF scheme.
Ahlborg et al., 1994	Develops first set of global consensus TEFs. Adds PCBs, including di-ortho congeners.
van den Berg et al., 1998	Develops second set of global consensus TEFs. Uses database compiled by the Karolinska Institute. Deletes di-ortho PCBs from the concept. Recognizes that TEFs for fish and birds need to be differentiated from humans. Acknowledges that in vivo results are more important than in vitro results.
U.S. EPA, 2000	Supplemental guidance for chemical mixtures risk assessment describes TEF and Relative Potency Factor methods. Endorses these for use by EPA.
U.S. EPA, 2003 (NAS Review draft)	This draft document recommends van den Berg et al. (1998) TEFs for EPA human health risk assessment. Provides details on historical development of TEFs.
Haws et al., 2006	Refines Karolinska Institute ReP database. Updates the literature. Deletes duplicate entries. Presents study exclusion criteria and deletes RePs based on studies not meeting the criteria. Presents statistical summaries of the RePs for each DLC.
van den Berg et al., 2006	Develops third set of global consensus TEFs. Uses Haws et al. (2006) database. Incorporates new literature including NTP (2006) study results. Holds stakeholder meeting at the beginning of the evaluation. Articulates shortcomings of the present TEF system. Identifies other potential compounds for inclusion in the TEF scheme.
NAS, 2006	Supports the use of the TEF approach by EPA to assess DLCs.
U.S. EPA, 2008	Recommends van den Berg et al. (2006) TEFs for EPA ecological risk assessments.
U.S. EPA, 2010 (this document)	Recommends van den Berg et al. (2006) TEFs for EPA human health risk assessments. Recommends the conduct of a sensitivity analysis be considered for major assessments as determined by U.S. EPA Regions or Program Offices.

AhR = aryl hydrocarbon receptor; NATO = North Atlantic Treaty Organization.

consequence of a specified definition of additivity, typically dose-addition or response addition.) To capture the uncertainty in these assumptions, all TEFs were provided as order-of-magnitude estimates, and the EPA described their application as a "useful interim approach" (U.S. EPA, 1989).

A set of guiding criteria were developed for TEF approaches (Barnes et al., 1991; U.S. EPA, 1991, 2000). These criteria included the development of TEFs through scientific consensus. The assignment of global consensus TEFs for the DLCs, including the dioxin-like PCBs, has been reevaluated as new data have become available (e.g., Ahlborg et al., 1994) and through consensus judgment of expert panels (e.g., WHO deliberations detailed in van den Berg et al., 1998, 2006). The TEF values published in van den Berg et al. (1998) were recommended for use by EPA in its National Academy of Science (NAS) review draft dioxin reassessment (U.S. EPA, 2003). In its review, NAS supported the use of the TEF approach (NAS, 2006, p. 8), stating that "Even with the inherent uncertainties, the committee concludes that the TEF methodology provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative potency of DLCs."

In 2005, a WHO expert panel updated TEF values for DLCs (van den Berg et al., 2006). They reaffirmed the characteristics necessary for inclusion of a compound in the WHO's TEF approach (van den Berg et al., 1998). These include:

- Structural similarity to polychlorinated dibenzo-*p*-dioxins or polychlorinated dibenzofurans;
- Capacity to bind to the aryl hydrocarbon receptor (AhR);
- Capacity to elicit AhR-mediated biochemical and toxic responses; and
- Persistence and accumulation in the food chain.

van den Berg et al. (2006) also reevaluated the support for assuming dose additivity and observing parallel dose-response curves. Evaluations of a number of studies of DLCs, including a mixture study from the National Toxicology Program that evaluated neoplastic and non-neoplastic endpoints (Walker et al., 2005), led the panel to state that the observed toxicity is consistent generally with these two assumptions underlying the TEF approach. In addition, the

NAS supported the use of an additivity assumption in its report on EPA's NAS review draft dioxin reassessment (U.S. EPA, 2003), concluding that "from an overall perspective, this assumption appears valid, at least in the context of risk assessment. Additivity in biochemical and toxic responses by the indicated DLCs has been supported by numerous controlled mixture studies in vitro and in vivo and is scientifically justifiable" (NAS, 2006, p. 80).

The TEF values were revised further by evaluating new toxicological data in conjunction with statistical summaries of available in vivo RePs formed using a mammalian ReP database (Haws et al., 2006). The database was comprised of ReP values from all identified studies that could yield an estimate of a ReP for a DLC; the RePs were not weighted according to study characteristics (e.g., in vivo, in vitro, chronic, acute, etc.). Haws and collaborators extended the original WHO ReP database, developed at the Karolinska Institute (ReP_{1997} database) in which some studies were represented more than once in the form of dissertations, conference proceedings, and/or peer-reviewed publications.[5] In the development of a refined ReP database, Haws et al. (2006) applied a set of study exclusion criteria to the ReP_{1997} database to identify RePs that likely provided "the most representative measure of a biological response." If a study met any of the exclusion criteria, the RePs derived from the study were not included in the quantitative analyses of all RePs. Haws et al. (2006) modified the ReP_{1997} database using the following exclusion criteria:

- Replicate RePs, when RePs from the same original study were presented in multiple publications.
- Multiple RePs from a single study that used different assays to measure the same response. In this case an effort was made to identify the single most representative ReP from a study.
- Study included only a single dose level of test and/or reference compound.
- Data omitted from the final peer-reviewed publication.

[5]The ReP_{1997} database was used in the WHO-European Centre for Environmental Health (ECEH)/International Programme on Chemical Safety (IPCS) TEF evaluation in 1997 and included not only published manuscripts, but also manuscripts in press, conference proceedings, theses, dissertations, and unpublished studies through June of 1997 that compared compounds to TCDD or PCB 126. Since the ReP_{1997} database was intended to be all inclusive, some studies are represented more than once in the form of dissertations, conference proceedings, and/or peer-reviewed publications.

- Authors indicated in the original publication that the ReP is not valid due to experimental problems.
- Data entry errors.
- ReP based on replicates in an in vitro study (average value calculated and retained).
- ReP based on non-AhR-mediated response.
- ReP based on nonmammalian species.
- Response for test or reference compound not statistically different from controls and not biologically meaningful.
- Reference compound (e.g., TCDD) not included in study or in identical study from the same laboratory.
- Multiple RePs derived from the same data using different calculation techniques.
- Multiple RePs reported for laboratory validation study (samples sent to two different labs for analysis and RePs calculated for both).
- Multiple RePs calculated based on different test conditions.
- RePs based on data at end of study and at end of some extended recovery period.
- ReP based on mixtures study.
- ReP from an unpublished study that could not be obtained.

The most recent WHO TEFs were developed using a refined approach. The WHO expert panel considered data from Haws et al. (2006) who present summary statistics of the RePs for each DLC, calculated from the assembled in vivo and in vitro studies that were not eliminated by the exclusion criteria. For each individual DLC, the WHO expert panel examined where the existing TEF value from van den Berg et al. (1998) fell within that DLC's in vivo ReP statistical summary developed in Haws et al. (2006). If it fell above the 75th percentile of the ReP statistical range, then they reviewed the basis of the 1998 TEF value, evaluated whether new data would impact the TEF and either confirmed the 1998 value or derived an updated TEF value. If it fell below the 75th percentile, the panel examined the database to identify the RePs having the most influence on the TEF value, evaluated the new data, and derived an updated TEF value (van den Berg et al., 2006). Because the ReP statistical ranges were unweighted relative to study type

and quality, the TEFs were determined using point estimates from toxicological studies, not by using specific points within the ReP ranges. A stepwise scale was used to assign the TEFs using half order of magnitude increments on a logarithmic scale (e.g., 0.03, 0.1, 0.3, etc.) instead of the increments used in previous efforts (e.g., 0.01, 0.05, 0.1, etc.), with uncertainty assumed to be at least ± half a log.[6]

[6]For example, the uncertainty for a TEF of 0.1 can be described as being within the interval of 0.03 and 0.3, and for a TEF value of 0.3, within an interval of 0.1 and 1. These estimates are generated by multiplying (dividing) the TEF value by half a log (i.e., 3.16).

UNCERTAINTIES IN THE TEF APPROACH

As is true for any risk assessment approach, uncertainties exist relative to data quality and evaluation, strength of biological rationale, and ability to determine whether the assumptions of the method being applied have been met. Application of the TEF approach to the human health risk assessment of DLCs carries with it some of these uncertainties which have been discussed in detail elsewhere in the literature. (For example, see discussions in Haws et al. [2006], NAS [2006], EPA [2000, 2003], and van den Berg et al. [1998, 2006].) The following uncertainties associated with application of the TEF approach are briefly described for the reader:

UNCERTAINTY IN TEF METHOD ASSUMPTIONS

- Dose additivity under the TEF method assumes a common mode of toxic action mediated through AhR binding and downstream biochemical and toxic responses. There is some evidence suggesting that some toxicities associated with some DLCs may be mediated through other ligands and processes (i.e., not mediated through the AhR). Effects mediated by other mechanisms (AhR independent) are not accounted for by the TEF method.

- Dose additivity under the TEF method assumes parallel dose-response curves. This is supported by some empirical data, but, in practice, parallelism is difficult to show for all DLCs and exposure scenarios, particularly in the low response region of most interest in environmental risk assessment.

- Dose additivity under the TEF method assumes that toxicological interactions are not occurring at environmental levels of the DLCs. Some data suggest that combined exposures of some DLCs may have antagonistic, rather than additive, effects; these could be species-specific. It may also be noted that joint toxic action of dioxins with non dioxin-like compounds could result in additive or nonadditive responses.

- Under the TEF method, the TEF of a DLC is assumed to be equivalent for all exposure scenarios, for all end points of concern, and all are full agonists. The ranges of RePs shown in the Haws et al. (2006) database demonstrate the uncertainty in this assumption as the ranges represent RePs from various study types and endpoints.

- Under the TEF method, it is assumed that RePs from animal studies are predictive of RePs in humans. However, the human AhR demonstrates some differences when compared to the AhR from experimental animal species.

UNCERTAINTY IN THE PROCESSES AND DATA USED TO DERIVE TEFs

- Expert scientific judgment, which depends on the knowledge and evaluations of the expert scientists involved, was used to select the DLCs included in the WHO TEF approach by evaluating experimental data against specific criteria (van den Berg et al., 2006). It may be noted that not all of the DLCs identified in releases from anthropogenic sources are included.

- Expert judgment and a consensus process were used to derive the WHO 2005 TEFs (van den Berg et al., 2006), including evaluation of information from the Haws et al. (2006) database.

- The kinds of information available for comparing the responses to individual DLCs to those of the index compound are highly variable across chemicals, including many types of and numbers of in vivo (including different test species) and in vitro studies. In addition, a number of different methods are employed to calculate REP values (Haws et al., 2006). (See additional discussions of this below under the section on Sensitivity Analysis Limitations.)

The uncertainty in TEQ estimates and in the TEF methodology accounts for only some of the overall uncertainty in a risk assessment of DLCs. TEQ uncertainty only pertains to the confidence associated with the estimation of TCDD equivalents in a mixture. There is also uncertainty associated with assessing exposures to environmental mixtures of TCDD and DLCs and with quantitatively linking health effects to the TCDD and DLC exposures. In addition, the value of a TEQ is highly dependent on the DLC exposure estimates used in the TEQ calculations.

RECOMMENDATIONS

When data on a whole mixture or a sufficiently similar mixture are not available for DLCs, the EPA recommends use of the WHO consensus mammalian TEF values from van den Berg et al. (2006) in the assessment of human health risks posed by exposure to mixtures of TCDD and DLCs, using TCDD as the index chemical. These TEFs are presented in Table 2. The TEF methodology is most applicable to situations where exposures are predominantly to mixtures of dioxins, furans and PCBs, and the goal of the assessment is to analyze the health risks posed by the mixture, not from exposure to individual compounds or single classes of compounds. Thus, other approaches may be considered when exposures are to single compounds or chemical classes.[7]

The EPA agrees with van den Berg et al. (2006) that the TEFs are most appropriate for dioxin exposures via the oral exposure route. The bioavailability of DLCs encountered through various sources of oral exposure needs to be evaluated in risk analyses. The TEFs may be applied to other exposure routes (i.e., dermal or inhalation), as an interim estimate or as a component of the sensitivity analysis, assuming exposures to DLCs via these routes can be quantified. Uncertainties associated with such applications should be identified. EPA recommends that, if considered in an assessment, the fractional contribution of oral, dermal, and inhalation route exposures to the predicted TEQ be identified.

TCDD and DLCs are associated with several different human health effects. Nearly all TCDD and DLC experimental data appear to be consistent with the hypothesis that binding to the AhR is the first step in a series of biochemical, cellular, and tissue changes that ultimately lead to toxic responses observed in both experimental animals and humans. The general basis for the TEF scheme is the assumption that the AhR mediates most if not all of the dioxin-like biological and toxic effects induced by compounds included in the WHO 2005 TEF approach (Safe, 1990; Okey et al., 1994; Birnbaum, 1994; Hankinson, 1995). Binding to the receptor

[7]For example, if the exposure is dominated by the single class of PCBs, then an alternative approach for evaluating human health risk might include use of the PCB cancer slope factors on Integrated Risk Information System (U.S. EPA, 1997). Also, when PCB exposures do not involve significant amounts of PCDDs and PCDFs, EPA (1996) provides another alternative methodology that might be useful for PCB mixture cancer dose-response assessment. However, in these cases, risks associated with other chemical exposures, i.e., not PCBs, would still need to be addressed.

Table 2. Recommended toxicity equivalence factors (TEFs) for human health risk assessment of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls

Compound	TEF
Polychlorinated dibenzo-*p*-dioxins (*PCDDs)*	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
Polychlorinated dibenzofurans (*PCDFs)*	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.0003
Polychlorinated biphenyls* (*PCBs)*	
3,3',4,4'-TCB (77)	0.0001
3,4,4',5-TCB (81)	0.0003
3,3',4,4',5-PeCB (126)	0.1
3,3',4,4',5,5'-HxCB (169)	0.03
2,3,3',4,4'-PeCB (105)	0.00003
2,3,4,4',5-PeCB (114)	0.00003
2,3',4,4',5-PeCB (118)	0.00003
2',3,4,4',5-PeCB (123)	0.00003

Table 2. Recommended toxicity equivalence factors (TEFs) for human health risk assessment of polychlorinated dibenzo-p-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls (continued)

Compound	TEF
2,3,3',4,4', 5 -HXCB (156)	0.00003
2,3,3',4,4',5'-HxCB (157)	0.00003
2,3',4,4',5,5'-HxCB (167)	0.00003
2,3,3',4,4',5,5'-HpCB (189)	0.00003

*Note: TEFs that were previously assigned to PCB 170 and PCB 180 (Ahlborg et al., 1994) were withdrawn during the WHO-ECEH/IPCS TEF re-evaluation in 1997, and a TEF for PCB 81 was established, such that the number of PCB compounds with TEFs assigned was reduced from 13 to 12 (van den Berg et al., 1998). The numbers in parentheses following each PCB are the PCB congener numbers.

Source: van den Berg et al. (2006); WHO's Web site on dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/.

appears to be necessary—but not sufficient—to generate the wide variety of toxic effects caused by dioxin-like halogenated aromatic hydrocarbons (Sewall and Lucier, 1995; DeVito and Birnbaum, 1995). In this document EPA assumes that all cancer and noncancer effects of TCDD and DLCs are AhR dependent. The EPA recommends these TEFs be used for all cancer and noncancer effects that appear to be mediated through AhR binding by the DLCs. EPA recognizes that this issue will require further evaluation as additional toxicity data become available. Eventually, endpoint-specific TEFs or separate TEFs for systemic toxicity and carcinogenicity endpoints may need to be developed.

van den Berg et al. (2006) also identified a number of candidate compounds that may need to be included in future developments of TEFs for DLCs:

- PCB 37
- Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans (PBDFs)
- Mixed halogenated dibenzo-*p*-dioxins and mixed halogenated dibenzofurans
- Hexachlorobenzene

- Polychlorinated naphthalenes and polybrominated naphthalenes
- Polybrominated biphenyls

EPA will consider an update of the recommendations in this document when TEFs for these candidate compounds are developed. At a minimum, if occurrence or exposure data are available for these candidate compounds, this information should be included as part of a qualitative risk characterization.

For analytic transparency, the EPA recommends that the fraction of the TEQ attributable to each PCDD, PCDF, or PCB compound be identified in the risk characterization (Table 2 lists the DLCs considered to be members of PCDD, PCDF, or PCB groups.) Further, the contributions of each chemical class, i.e., the PCDDs, PCDFs, and dioxin-like PCBs, should also be identified. Alternatively, the analysis could examine 2,3,7,8-TCDD alone, all dioxin congeners, and the dioxin-like compounds (PCBs and PCDFs) in three separate analyses. The compounds and class(es) making the largest contributions to the TEQ should be specified as appropriate to the assessment (see example in Text Box 1). In addition, the implications of the fraction of the TEQ attributable to TCDD should be discussed in the analyses because the dose-response data for TCDD are used to evaluate risks, and the confidence in the risk estimate increases with increases in the fraction of the TEQ attributable to TCDD. Finally, if multiple routes are considered in an assessment, the fractional contribution of the compounds and class(es) to each exposure route to the predicted TEQ should be identified.

Text Box 1. Example Risk Characterization

U.S. EPA (2003) notes that the majority of the TEQ (based on van den Berg et al., 1998) from dietary exposures is typically associated with the concentrations of only five compounds (i.e., TCDD, 1,2,3,7,8-PCDD, 2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDD, PCB 126) whose ReP variability appears to be small relative to other compounds.* Thus, if dietary exposures are important to the assessment being conducted, the fraction of the TEQ attributable to these five compounds should be presented and discussed in the risk characterization.

*Note that the TEF for 2,3,4,7,8-PeCDF changed from 0.5 to 0.3 from van den Berg et al., 1998 to 2006, respectively.

SENSITIVITY ANALYSIS

The EPA recommends that, for major risk assessments, as determined by U.S. EPA Program Offices or Regions, the conduct of a sensitivity analysis be considered to illustrate the impact the TEFs have on the TEQ value, which is consistent with good risk assessment practices (U.S. EPA, 2000). While ideally a full quantitative uncertainty analysis is desirable, currently

available ReP data that could be used to characterize the distributions of the TEFs are not suitable for use in simulation procedures (e.g., a Monte Carlo analysis) that are typically undertaken. Characterization of the underlying statistical distributions of the ReP data would be needed as input to a quantitative uncertainty analysis; the true probability distributions of the TEFs are not known at this time. The limitations in both the underlying ReP data and in the ability to statistically analyze them preclude a detailed evaluation of the various sources of heterogeneity inherent in a quantitative analysis of uncertainty. However, insightful sensitivity analyses can be conducted using estimated ranges of the TEFs.

A TEF sensitivity analysis has at least two purposes: (1) to identify plausible upper and lower estimates of the TEQ to assess the potential range the TEQ may have, and (2) to identify the influence of TEF values for specific compounds on the TEQ. One quantitative approach for identifying upper and lower TEQ estimates is presented in Eq. 2 and 3 below for *n* compounds with TCDD represented by compound $i = 1$ (see discussion of limitations of this approach below).

$$TEQ_U = \sum_{i=1}^{n} (C_i \times TEF_{iU}) \qquad \text{(Eq. 2)}$$

$$TEQ_L = \sum_{i=1}^{n} (C_i \times TEF_{iL}) \qquad \text{(Eq. 3)}$$

where:

TEQ_U = upper estimate of TEQ range

TEQ_L = lower estimate of TEQ range

C_i = concentration of the *i*th individual compound

TEF_{iU} = upper estimate of the *i*th compound's TEF; for $I = 1$, $TEF_{1U} = 1$

TEF_{iL} = lower estimate of the *i*th compound's TEF; for $I = 1$, $TEF_{1L} = 1$.

For the TEQ_U and TEQ_L estimates that are generated using Eq. 2 and 3, the fraction of the TEQ attributable to TCDD and to each DLC should be identified.

EPA is aware of two possible data choices for identifying compound specific TEF_{iU} and TEF_{iL} values. First, van den Berg et al. (2006) state that the TEFs are assumed to have

uncertainty of at least ± half a log (i.e., 3.16); thus, multiplying and dividing the compound specific TEFs by 3.16 could provide estimates of TEF_{iU} and i, respectively.

Second, the EPA is aware that Haws et al. (2006) has summarized statistical descriptions of the ReP values. Although limited to the available ReP data (i.e., not necessarily an unbiased sample of equivalence factors), the ReP ranges developed by Haws et al. (2006) may provide another source of data for TEF_{iU} and TEF_{iL} values to use in Eq. 2 and 3. Tables 3 and 4 present specific percentiles of the Haws et al. (2006) statistical summaries for the RePs derived from in vivo data and combined in vitro and in vivo data, respectively. The values for TEF_{iU} and TEF_{iL}, for example, could be based on the minimum and maximum data, the 10^{th} and 90^{th} percentiles, or the interquartile ranges from either Tables 3 or 4. Over time, this set of ReP values is expected to change with the availability of additional relevant studies.

To identify the influence of specific compounds on the TEQ, EPA recommends that the list of compounds that are most influential to the TEQ, as defined in Eq. 1, be further explored. For each of these, the sensitivity of the TEQ to changes in the TEF values for the individual compounds may be conducted (i.e., varying the TEF value for one compound at a time). The same statistical ranges described above can be used to identify alternative TEF values.

SENSITIVITY ANALYSIS LIMITATIONS

The suggested summations of TEF_i times C_i should not be interpreted as upper or lower bounds on confidence limits for the TEQ. These calculations only provide crude estimates of the range of the TEQ, and they are useful for comparing the impact that the TEF_i have on the TEQ in a sensitivity analysis. A summation using a specific percentile does not result in an estimate of the same percentile of the TEQ, but would likely overestimate that percentile for upper bound estimates and likely underestimate that percentile for lower bound percentiles. Thus, an overestimation of the TEQ range will increase as higher (lower) TEF percentiles are used in the summation.

Issues with the assignment of the WHO 2005 TEFs (van den Berg et al., 2006) and the construction of the Haws et al. (2006) ReP database preclude the conduct of a quantitative uncertainty analysis and the calculation of confidence limits. Both of these issues may be important in interpreting the results of a sensitivity analysis. The WHO 2005 individual TEFs are not central tendency estimates of the available values (van den Berg et al., 2006), but instead

Table 3. Percentiles of in vivo ReP values

Congener	*n*	min	0.1	0.25	0.5	0.75	0.9	max	2005 TEF
1,2,3,4,6,7,8-HpCDD	12	0.001	0.004	0.007	0.01	0.01	0.02	0.04	0.01
1,2,3,4,6,7,8-HpCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01
1,2,3,4,7,8,9-HpCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01
1,2,3,4,7,8-HxCDD	15	0.008	0.03	0.05	0.06	0.09	0.1	0.4	0.1
1,2,3,4,7,8-HxCDF	6	0.01	0.03	0.04	0.05	0.07	0.1	0.2	0.1
1,2,3,6,7,8-HxCDD	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.1
1,2,3,6,7,8-HxCDF	11	0.003	0.01	0.02	0.08	0.09	0.1	0.2	0.1
1,2,3,7,8,9-HxCDD	1	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.1
1,2,3,7,8,9-HxCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.1
1,2,3,7,8-PeCDD	36	0.04	0.1	0.2	0.4	0.6	0.8	2	1
1,2,3,7,8-PeCDF	20	0.003	0.009	0.01	0.02	0.08	0.1	1	0.03
2,3,4,6,7,8-HxCDF	3	0.02	0.02	0.02	0.02	0.06	0.08	0.1	0.1
2,3,4,7,8-PeCDF	82	0.007	0.05	0.1	0.2	0.3	0.7	4	0.3
OCDD	1	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003
OCDF	6	0.000004	0.00002	0.00004	0.00008	0.0006	0.001	0.002	0.0003
PCB105	16	0.0000005	0.000002	0.000009	0.00004	0.0001	0.001	0.002	0.00003
PCB114	2	0.0002	0.0002	0.0003	0.0003	0.0004	0.0004	0.0005	0.00003
PCB118	15	0.0000004	0.000002	0.000007	0.00002	0.00005	0.001	0.002	0.00003
PCB123	2	0.00003	0.00004	0.00004	0.00004	0.00005	0.0001	0.0001	0.00003
PCB126	86	0.0001	0.02	0.06	0.1	0.2	0.4	0.9	0.1

Table 3. Percentiles of in vivo ReP values (continued)

		Percentile							
Congener	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
PCB156	16	0.000002	0.000005	0.00003	0.00006	0.0005	0.09	0.4	0.00003
PCB157	2	0.0004	0.0006	0.0007	0.001	0.001	0.002	0.002	0.00003
PCB167	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.00003
PCB169	15	0.000002	0.0004	0.003	0.02	0.2	0.6	0.7	0.03
PCB189	3	0.00004	0.00004	0.00005	0.00006	0.0001	0.0002	0.0002	0.00003
PCB77	16	0.000002	0.000006	0.00001	0.00006	0.0001	0.02	0.04	0.0001
PCB81		N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.0003
TCDF	17	0.006	0.008	0.01	0.03	0.1	0.3	0.5	0.1

Source: Haws et al. (2006) 2004 ReP Database, Figure A-4.

Table 4. Percentiles of combined in vivo and in vitro ReP values

Percentile									
Compound	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
1,2,3,4,6,7,8-HpCDD	18	0.001	0.004	0.01	0.01	0.03	0.04	0.1	0.01
1,2,3,4,6,7,8-HpCDF	2	0.02	0.05	0.1	0.2	0.2	0.3	0.3	0.01
1,2,3,4,7,8,9-HpCDF	2	0.02	0.02	0.02	0.03	0.04	0.04	0.04	0.01
1,2,3,4,7,8-HxCDD	21	0.01	0.04	0.05	0.08	0.1	0.4	0.6	0.1
1,2,3,4,7,8-HxCDF	13	0.01	0.04	0.04	0.07	0.3	0.5	4	0.1
1,2,3,6,7,8-HxCDD	5	0.03	0.03	0.04	0.04	0.06	0.1	0.2	0.1
1,2,3,6,7,8-HxCDF	18	0.003	0.01	0.03	0.07	0.1	0.1	0.2	0.1
1,2,3,7,8,9-HxCDD	6	0.01	0.02	0.03	0.05	0.06	0.07	0.07	0.1
1,2,3,7,8,9-HxCDF	2	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.1
1,2,3,7,8-PeCDD	45	0.04	0.1	0.2	0.4	0.6	0.8	2	1
1,2,3,7,8-PeCDF	28	0.003	0.01	0.01	0.05	0.1	0.1	1	0.03
2,3,4,6,7,8-HxCDF	10	0.01	0.01	0.04	0.2	0.3	0.3	0.3	0.1
2,3,4,7,8-PeCDF	99	0.01	0.05	0.1	0.2	0.5	1	4	0.3
OCDD	6	0.0003	0.0003	0.0003	0.0003	0.002	0.003	0.003	0.0003
OCDF	9	0.000004	0.00003	0.00004	0.001	0.002	0.002	0.003	0.0003
PCB105	26	0.0000005	0.000005	0.00001	0.0001	0.0003	0.002	0.07	0.00003
PCB114	8	0.0001	0.0002	0.0002	0.001	0.001	0.002	0.002	0.00003

Table 4. Percentiles of combined in vivo and in vitro ReP values (continued)

Percentile									
Compound	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
PCB118	25	0.0000004	0.000002	0.00001	0.00002	0.0005	0.002	0.08	0.00003
PCB123	6	0.000003	0.00001	0.00002	0.00004	0.0001	0.0004	0.0007	0.00003
PCB126	115	0.0001	0.01	0.05	0.1	0.2	0.4	0.9	0.1
PCB156	30	0.000002	0.00001	0.00004	0.0001	0.001	0.2	0.5	0.00003
PCB157	9	0.00004	0.0001	0.0001	0.0004	0.001	0.002	0.002	0.00003
PCB167	5	0.000002	0.000005	0.00001	0.00001	0.00001	0.0004	0.001	0.00003
PCB169	30	0.000002	0.0007	0.002	0.01	0.06	0.5	0.8	0.03
PCB189	5	0.000002	0.000005	0.00001	0.00004	0.00006	0.0001	0.0002	0.00003
PCB77	49	0.000002	0.00002	0.0001	0.001	0.02	0.1	0.5	0.0001
PCB81	12	0.00004	0.0006	0.004	0.01	0.01	0.02	0.05	0.0003
TCDF	30	0.01	0.01	0.03	0.08	0.2	0.3	0.6	0.1

Source: Haws et al. (2006) 2004 ReP Database, Figure A-2.

are assigned based on professional judgment using both information from the Haws et al. (2006) database and from the available toxicology data; thus, these TEFs cannot be evaluated using statistics relevant to a mean or median value.

Haws et al. (2006) discuss the limitations of the current ReP database for use in quantitative uncertainty analysis. The RePs were calculated using various approaches, ranging from comparing dose-response curves, to developing ratios of effective doses that cause an effect in 50% of the test units (ED_{50s}), to estimating values from graphs of dose-response data. The RePs also represent a wide variety of study types and endpoints, including biochemical changes, systemic toxicity and carcinogenicity; some of these data may provide estimates that are more consistent than others with individual PCDD, PCDF, or PCB compound toxicity at higher levels of biological organization and such considerations will need to be included in a risk characterization. Finally, Haws et al. (2006) note a number of issues associated with the dose-response data (e.g., nonparallel dose-response curves, differences in maximal response among PCDD, PCDF, or PCB compounds within a study, incomplete dose-response data due to insufficient dose levels). In addition, the number of RePs available varies widely across the congeners from $n = 2$ to $n = 115$ RePs. Thus, the Haws et al. (2006) database provides "statistical descriptions," not probability distributions, as the RePs in the database are not unbiased random samples of TEF values.

Although EPA recognizes the limitations associated with the use of the Haws et al. (2006) database in sensitivity analyses, EPA believes the benefits associated with the conduct of such an analysis outweigh the limitations. The development of a more refined ReP database and additional examination of the uncertainties inherent in a TEF process would improve TEF-based risk assessments.

CONCLUSIONS

When whole mixture data or data on a sufficiently similar mixture are not available for DLC exposures, the EPA recommends use of the consensus mammalian TEF values from van den Berg et al. (2006) in the assessment of human health risks posed by exposures to mixtures of TCDD and DLCs (see Table 2), using TCDD as the index chemical. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. Further, while ideally a full quantitative uncertainty analysis is desirable, currently available ReP data that could be used to characterize the distributions of the TEFs are not suitable for use in simulation procedures that are typically undertaken. Because limitations in both the underlying ReP data and in the ability to statistically analyze them preclude conduct of a full quantitative uncertainty analysis of the TEQs, the EPA recommends that conduct of a sensitivity analysis be considered when using TEFs in major risk assessments, as determined by EPA Program Offices or Regions. In conducting a TEF-based risk assessment the EPA suggests addressing the key risk characterization recommendations that have been discussed in this document and are summarized in Table 5. The EPA will update all of these recommendations in the future based on the evaluation of new toxicity data for the DLCs, updates to the ReP database including statistical summaries of RePs for individual DLCs, and the results of new consensus processes undertaken to update the TEF approach.

Table 5. Summary of risk characterization recommendations for TEF applications

1) Apply the TEF methodology to situations where exposures are predominantly to mixtures of dioxins, furans, and PCBs, and the goal of the assessment is to analyze the human health risks posed by the mixture.
2) Identify the fraction of the TEQ attributable to TCDD, each DLC, and to each chemical class, i.e., the PCDDs, PCDFs, and dioxin-like PCBs. Alternatively, the analysis of chemical classes could examine separately the contributions from 2,3,7,8-TCDD alone, all dioxin congeners, and the dioxin-like compounds (PCBs and PCDFs) to the TEQ.
3) When it is deemed appropriate to apply TEFs to a multiroute exposure as an interim approach, identify the fractional contributions of oral, dermal, and inhalation route exposures to the predicted TEQ. Within each route of exposure, identify the fractional contribution of each congener to the predicted TEQ and identify the fraction of the TEQ associated with each chemical class.
4) Address the implications of the identified fractional contributions to the TEQ for the risk assessment being conducted, in particular, their impacts on the overall confidence in the analytic results.
5) Include occurrence or exposure data, if available, for the following compounds as part of a qualitative risk characterization:
    - PCB 37
    - Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans
    - Mixed halogenated dibenzo-*p*-dioxins and mixed halogenated dibenzofurans
    - Hexachlorobenzene
    - Polychlorinated naphthalenes and polybrominated naphthalenes
    - Polybrominated biphenyls
6) For major risk assessments as determined by EPA Program Offices or Regions, EPA recommends the conduct of a sensitivity analysis be considered to characterize the impact of TEF variability on the TEQ.
    - For the TEQ_U and TEQ_L estimates that are generated, identify the fraction of the TEQ attributable to TCDD, each DLC and each chemical class.
    - Identify the TEF_i values that are most influential to changing the TEQ estimate.

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