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Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds: EXTERNAL REVIEW DRAFT

Prepared by Risk Assessment Forum

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ABSTRACT

This document describes the U.S. Environmental Protection Agency's (U.S. EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing dioxin-like compounds (DLCs). Dioxin and DLCs are structurally and toxicologically related halogenated aromatic hydrocarbons. Traditionally, the Toxic Equivalency Factor (TEF) Methodology, a component mixture method, has been used to evaluate human health risks posed by these mixtures. The U.S. EPA recommends the use of the consensus TEF values for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and DLCs published in 2005 by the World Health Organization. The U.S. EPA recommends these TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by the DLCs including cancer and non-cancer effects. Using information that summarizes the range of relative toxicities of the DLCs, the U.S. EPA suggests that conduct of a sensitivity analysis be considered to illustrate the impact the TEFs have on the predicted risk. The U.S. EPA will update these recommendations in the future based on the evaluation of new toxicity data for

the 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	toxic equivalency factor
TEQ	toxic equivalence
U.S. 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 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 DLCs, TCDD is typically specified 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 equivalency but based on a single study, species, or matrix, etc., and not averaged to obtain a general toxic equivalency value.

TEFs: TEFs are estimates of compound-specific toxicity relative to the toxicity of an index chemical (typically, TCDD). TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data.

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

PREFACE

This document updates the U.S. EPA's approach for evaluating the human health risks from exposures to environmental media containing dioxin and dioxin-like compounds (DLCs). It is intended for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no binding effect on U.S. EPA or any regulated entity. Rather, it represents a statement of current policy. The U.S. 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 U.S. EPA's Risk Assessment Forum. The Risk Assessment Forum was established to promote scientific consensus on 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.

AUTHORS, TECHNICAL PANEL AND REVIEWERS [1]

This document was prepared by authors from U.S. EPA's Office of Research and Development and was then reviewed and completed by a Technical Panel under the auspices of U.S. EPA's Risk Assessment Forum.

AUTHORS

Belinda Hawkins, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Janet Hess-Wilson, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Glenn Rice (Document Co-lead), U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Jeff Swartout, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Linda Teuschler (Document Co-lead), U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268

TECHNICAL PANEL

Randy Wentsel (Chair), U.S. EPA, Office of Research and Development, Office of the Assistant Administrator, Washington, DC 20460
David E. Cooper, U.S. EPA, Office of Solid Waste and Emergency Response, Office of Superfund Remediation Technology Innovation, Washington, DC 20460
Michael DeVito, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Research Triangle Park, NC 27711
Tala Henry, U.S. EPA, Office of Prevention, Pesticides and Toxic Substances, Office of Pollution Prevention and Toxics, Risk Assessment Division, Washington, DC 20460
Margaret McDonough, U.S. EPA, Region 1, Boston, MA 02114
Marian Olsen, U.S. EPA, Region 2, New York, NY 10007
Glenn Rice, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Dan Stralka, U.S. EPA, Region 9, San Francisco, CA, 94105
Linda K. Teuschler, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268
Marlene Berg, U.S. EPA, Office of Solid Waste and Emergency Response, Office of Superfund Remediation Technology Innovation, Washington, DC 20460

RISK ASSESSMENT FORUM STAFF

Seema Schappelle, U.S. EPA, Office of the Science Advisor, Washington, DC 20460
Kathryn Gallagher, U.S. EPA, Office of the Science Advisor, Washington, DC 20460

[1] Additional reviewers are listed in Appendix A.

Gary Bangs, U.S. EPA, Office of the Science Advisor, Washington, DC 20460

INTRODUCTION

This document describes the U.S. Environmental Protection Agency's (U.S. EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing dioxin and dioxin-like compounds (DLCs). Dioxin and DLCs, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs), are structurally and toxicologically related halogenated dicyclic aromatic hydrocarbons.[2] Because the combined effects of these compounds have been found to be dose additive, the U.S. EPA has recommended use of the Toxic Equivalency Factor (TEF) Methodology and the World Health Organization's (WHO's) TEFs to evaluate the risks associated with exposure to mixtures of these compounds for human health (U.S. EPA, 1989, 2003) and ecological risk assessments (U.S. EPA, 2008). The WHO has used a process based on scientific consensus to develop TEFs for mammals, birds, and fish and has re-evaluated them on a schedule of approximately every five years (Ahlborg et al., 1994; Van den Berg et al., 1998, 2006; also see WHO's website for the dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/). In this document, the U.S. 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).

[2] 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 U.S. 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. 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, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is typically specified as the index chemical. The index chemical is well-studied toxicologically and must have a dose-response function to apply the methodology to an environmental mixture. The 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 toxicity measure from an individual toxicity assay is termed an estimate of relative potency

(ReP).[3] 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 (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, TCDD. These TCDD equivalent doses are then summed. To estimate risk associated with the mixture, this sum, which estimates the total index chemical equivalent dose for the mixture components considered, is compared to the dose-response function for TCDD.

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* DLCs compounds present in the mixture. The TEQ may be compared to the dose-response slope for TCDD and used to assess the risk posed by exposures to mixtures of DLCs.

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

[3] The term "relative effect potency" (ReP) also is used at times. We distinguish this term from 'relative potency factors' (RPF) method, which is a general dose additive method described in U.S. EPA (2000).

BACKGROUND

Initially, U.S. EPA (1989) recommended the use of the TEF approach for DLCs. Due to limitations in the available toxicity data for the DLCs, a number of additional assumptions were associated with this approach as implemented. Besides the inherent assumption of dose additivity, these assumptions included: the applicability of extrapolations from short-term bioassays to long-term health effects; similarities between interspecies metabolism; 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]). To capture the uncertainty in these assumptions, all TEFs were provided as order-of-magnitude estimates, and the U.S. EPA described their application as a “useful interim approach” (U.S. EPA, 1989).

A set of guiding criteria were developed subsequently 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 consensus TEFs for the DLCs 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 U.S. 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), 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 similarly shaped 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 U.S. 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" (NAS, 2006).

The TEF values were revised further by evaluating new toxicological data in conjunction with *in vivo* ReP distributions 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 an 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.[4] In the development of a refined ReP database, Haws et al. 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
- Authors indicated in the original publication that the ReP is not valid due to experimental problems
- Data entry errors

[4] 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.

- ReP based on replicates in an *in vitro* study (average value calculated and retained)
- ReP based on non-AHR-mediated response
- ReP based on non-mammalian 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 a statistical distribution 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 the *in vivo* ReP distribution developed in Haws et al. (2006). The panel then updated the TEF, or determined no change was needed, based on its position in the ReP distribution, on new toxicological data, and on expert judgment (Van den Berg et al., 2006). Because the ReP distributions were unweighted, the TEFs were determined using point estimates from toxicological studies, not by using specific points within the ReP distributions. 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.

RECOMMENDATIONS

The U.S. 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 exposure to mixtures of TCDD and DLCs. These TEFs are presented in Table 1.

The U.S. EPA agrees with Van den Berg et al. (2006) that the TEFs are most appropriate for dioxin exposures via the oral exposure route and that the bioavailability of DLCs encountered through other sources of exposure need to be evaluated in risk analyses. However, the TEFs may be applied to other exposure routes, (i.e., dermal or inhalation) as an interim estimate. U.S. EPA recommends that, if considered in an assessment, the fractional contribution of dermal and inhalation route exposures to the predicted TEQ be identified.

Dioxin and DLCs are associated with several different human health effects. The U.S. EPA recommends these TEFs be used for all cancer and non-cancer effects that are mediated through AHR binding by the DLCs. U.S. 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)

TABLE 1

Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessment of Polychlorinated Dibenzo-*p*-Dioxins, Dibenzofurans and Dioxin-Like Polychlorinated Biphenyls

Compound	TEF
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
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

TABLE 1 cont.

Compound	TEF
*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
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

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

*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).

- Mixed halogenated dibenzo-*p*-dioxins and mixed halogenated dibenzofurans
- Hexachlorobenzene
- Polychlorinated naphthalenes and polybrominated naphthalenes
- Polybrominated biphenyls

U.S. 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 in the risk analyses.

For analytic transparency, the U.S. EPA recommends that the fraction of the TEQ attributable to each PCDD, PCDF, or PCB compound be identified in the risk characterization and that the compounds making the largest contributions to the TEQ be specified as appropriate to the assessment. For example, 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.[5] 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. 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

[5] 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.

evaluate risks, and the confidence in the risk estimate increases with increases in the fraction of the TEQ attributable to TCDD.

The U.S. EPA suggests that a sensitivity analysis be considered when using TEFs in major risk assessments to illustrate the impact the TEFs have on the predicted risk, which is consistent with good risk assessment practices (U.S. EPA, 2000). However, the U.S. EPA recognizes that ranges and appropriate distributions of the uncertainty associated with each TEF will need to be developed to facilitate the conduct of advanced sensitivity analyses and uncertainty analyses. Although limited to the available ReP data (i.e., not necessarily an unbiased sample of equivalent factors), the ReP ranges developed by Haws et al. (2006) may provide a starting point for sensitivity analyses.

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 ED_{50s}[6] 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 with individual PCDD, PCDF, or PCB compound toxicity at higher levels of biological organization and such considerations will need to be included in the development of a TEF distribution. Finally, they note a number of issues associated with the dose-response data (e.g., non-parallel dose-response curves, differences in maximal response among PCDD, PCDF, or PCB compounds within a study, incomplete

[6]An ED_{50} is an effective dose that causes an effect in 50% of the test units.

dose-response data due to insufficient dose levels). Despite these challenges, U.S. EPA recognizes that 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

The U.S. 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 mixtures of TCDD and DLCs (Table 1). The U.S. EPA will update these recommendations in the future based on the evaluation of new toxicity data for the DLCs and the results of new consensus processes undertaken to update the TEF approach.

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APPENDIX A

RECOMMENDED TOXICITY EQUIVALENCY FACTORS (TEFS) FOR HUMAN HEALTH RISK ASSESSMENTS OF DIOXIN AND DIOXIN-LIKE COMPOUNDS DOCUMENT REVIEWERS

INTERNAL PEER REVIEWERS

Mike DeVito, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Research Triangle Park, NC 27711

Lynn Flowers, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC 20460

Glenn Suter, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH 45268