Evaluating the Toxicity and Assessing the Carcinogenic Risk of Environmental Mixtures Using Toxicity Equivalency Factors

Introduction

The toxicity equivalency factor (TEF) methodology was developed by the U.S. Environmental Protection Agency (EPA) to evaluate the toxicity and assess the risks of a mixture of structurally related chemicals with a common mechanism of action. A TEF is an estimate of the relative toxicity of a chemical compared to a **reference chemical.**

The Department of Ecology (Ecology) uses the TEF methodology to evaluate the toxicity and assess the risks for environmental mixtures of dioxins/furans and carcinogenicpolycyclic aromatic hydrocarbons (c-PAHs). This methodology may also be used to evaluate the toxicity of polychlorinated biphenyls (PCBs). The policies and procedures for applying the TEF methodology described here are consistent with the new rule amendments adopted by the Department of Ecology on October 12, 2007.

The adopted rule amends several sections for the rule to revise and update the risk policies for mixtures of dioxins/furans, CPAHs, and PCBs. Specifically, Ecology's adopted rule amendments require:

- That mixtures of dioxins and furans be considered a single hazardous substance when establishing and determining compliance with cleanup levels and remediation levels.

- That mixtures of cPAHs be considered a single hazardous substance when establishing and determining compliance with cleanup levels and remediation levels.

- That PCB mixtures be considered a single hazardous substance when establishing and determining compliance with cleanup levels and remediation levels.

- That people use the most current TEF values. These include:

Use of TEFs for dioxins/furans and PCBs recommended by the World Health Organization (Van den Berg, et al. 2006[1]) to characterize the toxicity of these mixtures.

Use of a potency equivalency factors (PEFs)[2] for cPAHs adopted by the California Environmental Protection Agency (California EPA, 2005) to characterize the toxicity of these mixtures.

- That people use the default gastrointestinal absorption fraction (ABI) of 0.6 to establish soil direct contact cleanup levels of dioxin and furan mixtures.

- That people use the physical-chemical properties of individual PAHs or dioxin/furan congeners when evaluation cross-media impacts.

This section of the Cleanup Levels and Risk Calculations (CLARC) Information System briefly describes the process for assessing the carcinogenic risk of mixtures using TEFs and provides the TEFs for mixtures of cPAHs, mixtures of dioxins/furans, and mixtures of PCBs.

Evaluating the toxicity and assessing of the Carcinogenic Risk of Mixtures of cPAHs

Polycyclic aromatic hydrocarbons (carcinogenic) or "cPAHs", as defined in WAC 173-340-200, are "those polycyclic aromatic hydrocarbons, PAHs, identified as Group A (known human) or B (probable human) carcinogens by the United States Environmental Protection Agency. These include benzo(a)pyrene, chrysene, dibenzo(a,h)anthracene, and indeno(1,2,3-cd)pyrene."

When establishing and determining compliance with cleanup levels and remediation levels for mixtures of cPAHs under the Model Toxics Control Act (MTCA) Cleanup Regulation (WAC 173-340-708(8)(e)), the mixture shall be considered a single hazardous substance. This means that a target cancer risk level of one in one million (10^{-6}) is used when calculating cleanup levels under Method B.

For mixtures of cPAHs, the reference chemical is **benzo(a)pyrene.** Benzo(a)pyrene was chosen as the reference chemical because the toxicity of the chemical is well characterized. The toxicity equivalency factor for each cPAH is an estimate of the relative toxicity of the cPAH compound compared to benzo(a)pyrene.

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[1] Source: Van den Berg et al. 2006. The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds

[2] Cal-EPA's term "Potency Equivalency Factor" is synonymous in concept to "Toxicity Equivalency Factor" and the two terms are used interchangeably here. CLARC will use "TEF" for the remainder to be consistent with the rule language.

The TEF methodology must be applied when determining compliance with cleanup and remediation levels established for mixtures of cPAHs. Although there may be toxicity values available in IRIS for selected c-PAHs, such as benzo(a)anthracene, CLARC no longer contains Method B or C soil cleanup levels for these individual chemicals but requires the application of the TEF methodology. When using the TEF methodology, at a minimum, the compounds in Table 1 must be analyzed for and included in the calculations.

Table 1: Toxicity Equivalency Factors (TEFs) For Minimum Required Carcinogenic Polycyclic Aromatic Hydrocarbons (cPAHs) Under WAC 173-340-708(e)

CAS Number	c-PAH	TEF (Unitless)[3]
50-32-8	Benzo(a)pyrene	1
56-55-3	Benzo(a)anthracene	0.1
205-99-2	Benzo(b)fluoranthene	0.1
207-08-9	Benzo(k)fluoranthene	0.1
218-01-9	Chrysene	0.01
53-70-3	Dibenzo(a,h)anthracene	0.1
193-39-5	Indeno(1,2,3cd)pyrene	0.1

Ecology may require additional compounds from the CalEPA list be included in the methodology, should site testing data or information from other comparable sites or waste types indicate that the additional compounds are potentially present at the site. (See Table 708-3, MTCA Rule adopted October 2007)

To establish cleanup levels and/or remediation levels protective of other media, such as soil levels protective of groundwater, the physical-chemical properties of individual carcinogenic cPAHs must be used. Ecology will prepare separate guidance addressing this calculation.

Evaluating the Toxicity and Assessing the Carcinogenic Risk For Mixtures of Dioxins/Furans

Mixtures of chlorinated dibenzo-p-dioxin (dioxins; CDDs) and chlorinated dibenzofurans (furans; CDFs) are complex environmental mixtures of 210 interrelated chemicals composed of different dioxins and furans. For mixtures of dioxins/furans, the reference chemical is **2,3,7,8 – tetrachlorodibenzo-p-dioxin (2,3,7,8 – TCDD)** because it is the most toxic and best-studied of the 210 CDDs and CDFs. EPA first adopted the TEF methodology as an interim procedure for

[3] Source: Cal-EPA, 2005. Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II Technical Support Document for Describing Available Cancer Potency Factors. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. May 2005

evaluation the toxicity and to assess the risks associated with exposures to dioxin and furan mixtures. The majority of state, federal and international environmental agencies currently use TEFs when evaluating the health risks posed by dioxin/furan mixtures.

When establishing and determining compliance with cleanup levels and remediation levels for mixtures of CDDs and CDFs under the MTCA Cleanup Regulation (WAC 173-340-708[8][d]), the mixture shall be considered a single hazardous substance. This means that a target cancer risk level of one in one million (10^{-6}) is used when calculating cleanup levels under Method B.

Although there may be toxicity values available in IRIS for selected dioxin/furan congeners (hexachlorodibenzo-p-dioxin mixture of 1,2,3,6,7,8-HxCDD and 1, 2, 3, 7, 8, 9-HxCDD), CLARC no longer contains Method B or C soil cleanup levels for these individual congeners but requires the application of the TEF methodology. When using the TEF methodology, each of the following compounds (congeners) in Table 2 must be analyzed for and included in the calculations.

Table 2: TEFs for Chlorinated dibenzo-p-dioxins (CDDs) and Chlorinated Dibenzofurans Congeners (CDFs) [Mammals Only]

CAS Number	Dioxin Congeners (CDDs)	TEF (Unitless)[4]
1746-01-6	2,3,7,8-Tetrachloro dibenzo-p-dioxin (2,3,7,8- TCDD)	1
40321-76-4	1,2,3,7,8-Pentachloro dibenzo-p-dioxin (1,2,3,7,8-PeCDD)	1
39227-28-6	1,2,3,4,7,8-Hexachloro dibenzo-p-dioxin (1,2,3,4,7,8-HxCDD)	0.1
57653-85-7	1,2,3,6,7,8- Hexachloro dibenzo-p-dioxin (1,2,3,6,7,8-HxCDD)	0.1
19408-74-3	1,2,3,7,8,9- Hexachloro dibenzo-p-dioxin (1,2,3,7,8,9-HxCDD)	0.1
35822-46-9	1,2,3,4,6,7,8- Hexachloro dibenzo-p-dioxin (1,2,3,4,6,7,8-HxCDD)	0.01
3268-87-9	1,2,3,4,6,7,8,9 - Octachloro dibenzo-p-dioxin (1,2,3,4,6,7,8,9 -OCDD)	0.0003
CAS Number	**Furan Congeners (CDFs)**	**TEF (Unitless)**
51207-31-9	2,3,7,8-Tetrachloro dibenzofuran (2,3,7,8-TCDF)	0.1
57117-41-6	1,2,3,7,8-Pentachloro dibenzofuran (1,2,3,7,8-PeCDF)	0.03
57117-31-4	2,3,4,7,8- Pentachloro dibenzofuran (2,3,4,7,8-PeCDF)	0.3
70648-26-9	1,2,3,4,7,8-Hexachloro dibenzofuran (1,2,3,4,7,8-HxCDF)	0.1
57117-44-9	1,2,3,6,7,8-Hexachloro dibenzofuran (1,2,3,6,7,8-HxCDF)	0.1
72918-21-9	1,2,3,7,8,9-Hexachloro dibenzofuran (1,2,3,7,8,9-HxCDF)	0.1
60851-34-5	2,3,4,6,7,8-Hexachloro dibenzofuran (2,3,4,67,8-HxCDF)	0.1
67562-39-4	1,2,3,4,6,7,8-Heptachloro dibenzofuran (1,2,3,4,6,7,8-HpCDF)	0.01
55673-89-7	1,2,3,4,7,8,9-Heptachloro dibenzofuran (1,2,3,4,7,8-HpCDF)	0.01
39001-02-0	1,2,3,4,6,7,8,9-Octachloro dibenzofuran (1,2,3,4,6,7,8-OCDF)	0.0003

[4] Source: Van den Berg et al. 2006. The 2005 World Health Organization Re-evaluation of Human and Mammailian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds. Toxicological Science 2006 93(2): 223-241;doi:10.1093/toxsci/kfl055.

To establish cleanup levels and/or remediation levels protective of other media, such as soil levels protective of groundwater, the physical-chemical properties of individual CDD and CDF congeners must be used. Ecology will prepare separate guidance addressing this calculation.

Evaluating the Toxicity and Assessing the Carcinogenic Risk For Mixtures of Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are a group of synthetic organic chemicals that include 209 individual chlorinated biphenyl compounds (known as congeners). Commercial mixtures of PCBs were manufacture in the United States from 1930 to 1977 under the trademark "**Aroclor**" followed by a four digit number. Usually the first two digits indicate the parent biphenyl molecule and the last two digits indicate the percent chlorine by weight. For example, Aroclor 1260 contains 12 carbon atoms (parent biphenyl molecule) and approximately 60 percent chlorine by weight. Aroclor 1016 is an exception to this nomenclature scheme, as it contains 12 carbon atoms and contains over 41 percent chlorine by weight. PCBs were used as coolants and lubricants in electrical equipment, such as capacitors and transformers, because of their inflammability, chemical stability, and insulating properties. There are no known natural sources of PCBs.

When establishing and determining compliance with cleanup levels and remediation levels for mixtures of PCBs under the MTCA Cleanup Regulation (WAC 173-340-7-8[8]), the mixture shall be considered a single hazardous substance. This means that a target cancer risk level of one in one million (10^{-6}) is used when calculating cleanup levels under Method B.

The MTCA rule provides for two options for assessing the cancer risk of PCB mixtures:

1) Samples are analyzed for total PCBs (aroclors), the entire PCB mixture is assumed to be equitoxic, and a cancer potency factor from EPA IRIS database is assigned to the mixture; OR
2) Samples are analyzed for PCB congeners and the toxicity and risks of the PCB mixture is assessed using Toxicity Equivalency Factors.

When using TEFs, use the toxicity equivalency factors from Table 3 to evaluate the toxicity and assess the risk for the 12 dioxin-like PCBs (4 non-ortho and 8 mono-ortho PCBs). The Cancer Potency Factor for 2, 3, 7, 8-TCDD (130,00 [mg/kg-day]-1) should be used to evaluate the toxicity and assess the cancer risks for dioxin-like PCBs.

Table 3: TEFs for Dioxin-Like Polychlorinated Biphenyls (PCBs)		
CAS Number	**Dioxin-Like PCBs**	**TEF (Unitless)[5]**
32598-13-3	3,3',4,4'-Tetrachlorobiphenyl (PCB 77)	0.0001
70362-50-4	3,4,4',5-Tetrachlorobiphenyl (PCB 81)	0.0003
32598-14-4	2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)	0.00003
74472-37-0	2,3,3,4,4',5-Pentachlorobiphenyl (PCB 114)	0.00003
31508-00-6	2,3',4,4',5-Pentachlorobiphenyl (PCB 118)	0.00003
65510-44-3	2',3,4,4',5-Pentachlorobiphenyl (PCB 123)	0.00003
57465-28-8	3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	0.1
38380-08-4	2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)	0.00003
69782-90-7	2,3,3',4,4',5'-Hexachlorobiphenyl (PCB 157)	0.00003
52663-72-6	2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167)	0.00003
32774-16-6	3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169)	0.03
39635-31-9	2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189)	0.00003

Ecology should be consulted regarding the evaluation of the toxicity and assessment of the risk for both dioxin-like and nondioxin-like PCBs. How the risk from non-dioxin like PCBs will be assessed is still evolving on a national level. After adoption of the rule amendments Ecology will continue to work with EPA Region 10 to clarify how the risks from dioxin-like and non-dioxin like PCBs will be assessed for Washington State. Below are two quotes from EPA regarding the procedures for assessing the risks from dioxin-like and non-dioxin like PCBs.

EPA Region 10 Guidance Memo (dated 4/17/07 – Recommendations for Human Health Risk-based Chemical Screening and Related Issues at EPA Region 10 CERCLA and RCRA Sites)

"The contribution of dioxin-like PCB congeners is important in the evaluation of risks associated with releases of PCBs, and in the development of PCB cleanups levels, as the evaluation of Aroclors or total PCBs alone may result in a mischaracterization of the mixture. As described on the IRIS web site for PCBs, risks from dioxin-like congeners can be evaluated separately from the rest of the mixture. Analyses of dioxin-like PCB congeners from at least a portion of media samples are strongly recommended by this office as the default procedure for estimating baseline risks and for developing and demonstrating compliance with cleanup levels."

EPA IRIS Database http://www.epa.gove/iris/subst/0294.htm)

[5] Source: Van den Berg et al. 2006. The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds. Toxicological Sciences 2006 93(2):223-241;doi:10.1093/toxsci/kfl055.

Although PCB exposures are often characterized in terms of Aroclors, this can be both imprecise and inappropriate. Total PCBs or congener or isomer analyses are recommended. When congener concentrations are available, the slope-factor approach can be supplemented by analysis of dioxin TEQs to evaluate dioxin-like toxicity. Risks from dioxin-like congeners (evaluated using dioxin TEQs) would be added to risks from the rest of the mixture (evaluated using slope factors applied to total PCBs reduced by the amount of dioxin-like congeners)."

Determining Toxicity Equivalent Concentrations

The mathematical expression to determine the toxicity equivalent concentration is provided below:

Characterizing C-PAH, Dioxin/Furan, &PCB Mixtures When Using TEFs

Total Toxicity Equivalence Concentration[6] (TTEC) = $\sum C_n * TEF_n$

Where:

TTEC = Total Toxicity Equivalent Concentration

C_n = Concentration of the individual congener or cPAH in the mixture

TEF_n = Toxic equivalency factor of the individual congener or CPAH associated with its respective mixture

The following steps should be taken to determine the toxicity equivalent concentration for mixtures of cPAHs, dioxins/furans, and dioxin-like PCBs:

1. Analyze the chemical mixture in a sample to determine the concentration of each congener/cPAH.
2. To obtain a toxicity equivalent concentration (TEC), multiply each congener/cPAH concentration identified in the sample by the corresponding TEF from the tables above for the respective mixture.
3. Add the products in step 2 to obtain the total toxicity equivalent concentration (TTEC) for the chemical mixture.
4. To determine compliance compare the total toxicity equivalent soil concentration (TTEC) for the chemical mixture with the applicable cleanup level for the reference chemical. For example, for mixtures of dioxins/furans and dioxin-like PCBs the reference chemical is 2,3,7,8 – tetrachlorodibenzo-p-dioxin (2,3,7,8 – TCDD) with a Method B cleanup level

[6] Also referred to as Total Toxicity Equivalence, TEQ, by U.S. Environmental Protection Agency.

13 ppt (13 ng/kg). Note that these cleanup levels for 2,3,7,8 – TCDD are for the protection of direct contact via soil ingestion exposure pathway with a gastrointestinal absorption fraction of 0.6. If another exposure pathway is driving the soil cleanup level, a different cleanup level would need to be used. For mixtures of cPAHs the reference chemical is a benzo(a)pyrene (BaP) with a Method B cleanup level of 0.137 mg/kg and a Method C cleanup level 18 mg/kg. Note that these cleanup levels for BaP are for the protection of direct contact via the soil ingestion exposure pathway.

Example

Consider a site where the soil is contaminated with a mixture of cPAHs and that soil cleanup levels are to be based on unrestricted land use (that is, Method B). Based on this scenario, the following steps should be followed to determine whether the soil concentrations exceed the cleanup level of a particular soil sample. Measured soil concentrations and calculations referred to in the following steps are presented in the table below.

Step 1: Analyze the cPAH mixture at the site to determine the presence of each cPAH [column 1] and the solid concentration of each cPAH (Column 2).

Step 2: For each cPAH identified at the site, multiply the soil concentration (Column 2) by the applicable TEF (Column 3) to obtain a toxicity equivalent soil concentration (TEC) (Column 4).

Step 3: Add the products in step 2 to obtain the total toxicity equivalent soil concentration (TTEC) for the cPAH mixture(=0.133 mg/kg).

Step 4: Compare the TTEC for the cPAH mixture (0.133 mg/kg) with the Method B cleanup level for benzo(a)pyrene (0.137 mg/kg rounded to 0.14 mg/kg).

Example TEF Calculations for Hypothetical c-PAHs Contaminated Site

C-PAH	Measured Soil Concentration (mg/kg)	Toxicity Equivalency Factor (TEF, Unitless)	Toxicity Equivalent Soil Concentration (mg/kg)
Benzo(a)pyrene	0.05	1.00	0.05
Benzo(a)anthracene	0.15	0.10	0.015
Benzo(b)fluoranthene	0.20	0.10	0.02
Benzo(k)fluoranthene	0.10	0.10	0.01
Chrysene	0.80	0.01	0.008
Dibenzo(ah,h)anthracene	0.20	0.10	0.02
Indeno(1,2,3-cd)pyrene	0.10	0.10	0.01
Sum	1.60		0.133 = TTEC

Conclusion: The TTEC for the c-PAH (0.133 mg/kg) of this particular soil sample does not exceed the Method B cleanup level for benzo(a)pyrene (0.137 mg/kg). Therefore, the cleanup level for benzo(a)pyrene has been met for this particular soil sample.