Dose Additivity Guidance

Acronyms

BaP	benzo(a)pyrene
BMD	benchmark dose
CEL	comparative effect level
CMG	common mechanism group
CNS	central nervous system
CTL	cleanup target level
F.A.C.	Florida Administrative Code
FDEP	Florida Department of Environmental Protection
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
HI	hazard index
ICED	index chemical-equivalent dose
NMC	N-methyl carbamates
NOAEL	no observed adverse effect level
OP	organophosphate
OPP	Office of Pesticide Programs
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-p-dioxin
PCDF	polychlorinated dibenzofuran
PNS	peripheral nervous system
RPF	relative potency factor
SAP	Scientific Advisory Panel
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF	toxicity equivalence factor
TEQ	toxic equivalency concentration
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

1. Introduction

This guidance document was developed to provide information on the use of dose additivity with regard to the cleanup of contaminated sites. Persons conducting site cleanup may use this approach or may propose an alternative approach based upon actual data on the interaction of site contaminants. Persons following Chapter 62-780, Florida Administrative Code (F.A.C.) "Contaminated Site Cleanup Criteria" should note that this approach supersedes the discussion of apportionment in the 62-780, F.A.C., referenced guideline "Technical Report: Development of Cleanup Target Levels (CTLs) for Chapter 62-777, F.A.C., Final" Appendix E, Section C, dated February 2005.

1.1 Purpose

This dose additivity guidance is intended to be used in the evaluation of risk to human health from exposure to chemical mixtures when comparing results to CTLs in Chapter 62-777, F.A.C., or when developing CTLs or alternative CTLs. Specifically, this guidance provides technical instruction applicable when polychlorinated dibenzo-*p*-dioxins/ polychlorinated dibenzofurans (PCDDs/PCDFs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and pesticide mixtures are present at a site. Although other methodologies are available for evaluating mixture toxicity, this guidance has been developed based on a component-based dose additivity approach suggested for use by the United States Environmental Protection Agency (USEPA) when whole mixture toxicity data are not available.

1.2 Applicability

Most cases of environmental contamination involve exposure to more than one chemical. In the absence of information indicating that chemicals interact chemically or biologically in a non-additive way (e.g., antagonistically or synergistically), their effects are assumed to be additive, i.e. their combined effect is equal to the sum of their individual effects. When assessing human health risk from contaminated media, additivity approaches can be used to predict the cumulative effect from exposure to multiple chemicals. Due to the nature of multi-chemical exposures, analyzing a specific mixture of chemicals can be complex (USEPA, 2000). This guidance represents the Florida Department of Environmental Protection's preferred methodology for evaluating mixture toxicity when comparing results to CTLs in Chapter 62-777, F.A.C., or when developing CTLs or alternative CTLs. It is applicable for all media where PCDD/PCDFs, PCBs, PAHs, or certain pesticide mixtures are present. This guidance does not explicitly address interactive effects other than dose additivity (e.g., antagonistic or synergistic effects).

2. Background: Dose Additivity versus Response Additivity

For assessing risk to chemical mixtures, the USEPA's chemical mixture guidance document (USEPA, 2000) recommends the use of whole mixture data. These are toxicity data derived from testing chemicals as a mixture. When whole mixture data are not available for a combination of chemicals of interest, which is often the case, USEPA recommends a component-based method (USEPA, 2010). There are two common component-based approaches for evaluating a mixture: dose additivity and response additivity. Dose additivity is the process of analyzing similarly acting chemicals and is a summation of exposure levels (doses). Response additivity, although not specifically

applicable to this guidance document, is the process of analyzing independently acting chemicals and is a summation of the exposure responses for each chemical (USEPA, 2000). These approaches are discussed in detail below.

2.1 Dose Additivity

Dose additivity is a method of mixture analysis for chemicals that have a common mechanism of toxicity and share similar dose response curves.   When they exhibit a common toxicological outcome, these chemicals are said to belong to a common mechanism group (CMG) (USEPA, 2003).

At a site where more than one chemical within a CMG is detected, risk can be calculated using the dose additivity method. In this method, concentrations (e.g., in soil or groundwater) for individual chemicals are scaled to an index chemical based upon comparative toxic potencies of the chemicals. The index chemical in a CMG is chosen based on an abundance of existing toxicological dose response data (USEPA, 2003). The comparative toxic potencies of the chemicals are expressed through relative potency factors (RPFs), which are calculated by dividing the equivalent toxic dose of the index chemical by the equivalent toxic dose of a given chemical in the CMG.

$$RPF = \frac{Equivalent\ Toxic\ Dose_{[Index\ Chemical]}}{Equivalent\ Toxic\ Dose_{[Chemical\ n]}}$$

The RPF for a given chemical is multiplied by the concentration of that chemical to produce an index chemical-equivalent dose (ICED). The ICEDs for all chemicals present are added together to express the total mixture dose in terms of an equivalent dose of the index chemical. The dose response curve of the index chemical is used to estimate the response from the total ICED (USEPA, 2000). From that response, risk from potential exposure to the CMG mixture can be quantified. For practical purposes, the risk to the total ICED is determined to be of concern if it is above the index chemical's CTL in a given environmental medium.

$$Total\ ICED = \sum Concentration_i \times RPF_i$$

2.2 Response Additivity

In contrast to dose additivity, response additivity is a method of mixture analysis for chemicals with functionally independent mechanisms of toxicity. Response additivity does not assume chemicals have similarly shaped dose response curves as does dose additivity (USEPA, 2000).

At a site where more than one chemical has hazardous effects on the same target organ or tissue, risk can be calculated using the response additivity method. In this method, risk from exposure to each chemical is quantified separately and then summed for chemicals that have similar endpoints. The total risk is then determined to be a concern if it is above a hazard index (HI) of one for non-carcinogens or a target risk level of 1.0E-06 for carcinogens. This guidance document does not address how to incorporate response additivity into a cleanup or risk assessment pursuant to 62-780, F.A.C.

$$Total\ Risk\ =\ \sum Risk_i$$

3. Common Uses of Dose Additivity

There are two terms used to express the comparative toxic potency of chemicals — RPFs and Toxicity Equivalence Factors (TEFs). Both are conceptually similar, but there are a few differences that make the use of one or another more appropriate in a given situation. A TEF is intended to apply to all exposure routes, exposure durations, and health effects of a chemical (USEPA, 2003). RPFs, in contrast, are used to compare potency among chemicals for specific health effects, and can be route-specific and intended to apply to certain exposure durations and even certain dose ranges. As explained below, TEFs are used to sum the risks of various cancers produced by PCDD/PCDF congeners regardless of the route of exposure or exposure duration. For pesticides, RPFs are used to sum the risk of specific non-cancer effects produced by classes of pesticides, such as cholinesterase inhibition, and are developed on a route-specific basis. Thus, while the basic concept is the same, the context determines whether potency differences are described through TEFs or RPFs.

3.1 PCDDs/PCDFs and PCBs

The USEPA recommends the use of World Health Organization (WHO) TEFs for quantifying cancer risk to mixtures of PCDDs, PCDFs, and dioxin-like compounds. In 2005, WHO reconfirmed that the toxicological effects from these mixtures were generally consistent with the use of the dose additivity approach. In 2010, the USEPA updated its TEFs for dioxin-like compounds by adopting the mammalian TEFs recommended in the WHO 2005 reevaluation (USEPA, 2010; van den Berg et al., 2006).

For PCDDs, PCDFs, and most dioxin-like compounds, the index chemical is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Therefore, comparative cancer potency for PCDD or PCDF congeners relative to TCDD are calculated by dividing the equivalent toxic dose of TCDD by the equivalent toxic dose of the congener.

$$TEF = \frac{Equivalent\ Toxic\ Dose_{[TCDD]}}{Equivalent\ Toxic\ Dose_{[Chemical\ n]}}$$

Similar to the RPF approach, once a congener TEF is calculated, it is multiplied by the individual congener concentration to produce the TCDD toxic equivalent concentration (TEQ). The TEQs for all carcinogenic congeners present are added together to express the total mixture concentration in terms of an equivalent concentration of TCDD. The TCDD cancer potency factor is used to estimate the response from the total TEQ. For practical purposes, the risk to the total TEQ is determined to be of concern if it is above the TCDD CTL in a given medium. PCDD/PCDF TEFs are listed in Table 1.

$$Total\ TEQ\ =\ \sum Concentration_i \times TEF_i$$

A dioxin equivalent conversion table for one or more samples is available at the FDEP website (http://www.dep.state.fl.us/waste/categories/wc/pages/ProgramTechnical

Support.htm). Because these chemicals are usually found in the environment as mixtures, it is reasonable to assume that when one PCDD/PCDF congener is detected, the other non-detected congeners are also present at non-zero concentrations. Therefore, when calculating dioxin equivalents, congeners that are not detected should be assumed to be present at one-half the detection limit. Further details on the treatment of congener data are included on the conversion table referenced above. An example calculation is shown in Table 2.

TEFs are also available to convert PCB congeners to TCDD equivalents (Table 1). Therefore, if concentrations of individual PCB congeners are known, it is possible to use the TEQ approach to assess cumulative risk posed by these contaminants. The TEF methodology is applicable 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 (USEPA, 2010). When exposures are to single classes of chemicals (e.g., PCBs), other approaches may be considered. For example, the USEPA has generated toxicity values for PCB mixtures (e.g., Aroclor mixtures) that could be used to evaluate risks from PCBs.

3.2 PAHs

Because carcinogenic PAHs have similar mechanisms of toxicity, the TEF approach for dose additivity can be used to quantify cancer risk from exposure to PAH mixtures (USEPA, 1993). The index chemical for PAHs is benzo(a)pyrene (BaP). The methodology for calculating the TEFs for the carcinogenic PAHs is the same as the method for calculating the TEF for PCDD/PCDFs. Comparative potencies of individual PAHs are calculated by dividing a toxic dose of BaP by the equivalent toxic dose of the PAH of interest. To determine total cancer risk from a mixture of PAHs, the concentration of each carcinogenic PAH is multiplied by its respective TEF to produce the BaP toxic equivalent concentration (TEQ). The TEQs for all PAHs present are added together to express the total mixture dose in terms of an equivalent concentration of BaP. The BaP cancer potency factor is used to estimate the response from the total TEQ. For practical purposes, the risk to the total TEQ is determined to be of concern if it is above the BaP CTL in a given medium. BaP TEFs are listed in Table 3.

A BaP equivalent conversion table for one or more samples is available at the FDEP website (http://www.dep.state.fl.us/waste/categories/wc/pages/ProgramTechnical Support.htm). Similar to dioxins, these chemicals are often found in the environment as mixtures. Therefore, when calculating BaP equivalents, congeners that are non-detected should be assumed to be present at one-half the detection limit. Further details on the treatment of congener data are included on the conversion table referenced above. An example calculation is shown in Table 4.

4. Dose Additivity for Pesticides

In addition to the common uses of the dose additivity approach discussed above, the USEPA has developed dose additivity information for five different pesticide classes as part of its efforts to develop cumulative risk assessment methods. In contrast to the PCDDs, PDCFs, PCBs, and PAHs, all of the toxic endpoints for dose additivity of pesticides are non-cancer effects.

4.1 Background

In 1996, the Food Quality Protection Act (FQPA) required the USEPA's Office of Pesticide Programs (OPP) to assess human health risk from multiple exposure pathways to more than one pesticide acting through a common mechanism of toxicity (USEPA, 2002a). The OPP evaluated six groups of pesticides (organophosphates, N-methyl carbamates, triazines, chloroacetanilides, pyrethrins and pyrethroids, and thiocarbamates and dithiocarbamates) for potential human health risks to multi-chemical and multi-pathway exposures through cumulative risk assessments. The OPP developed RPFs for organophosphates, N-methyl carbamates, pyrethrins and pyrethroids, and chloroacetanilides. A detailed summary of the OPP evaluations for each pesticide group is provided below, including the RPF where applicable. Following the summaries, Section 5 reviews the practical application for use of RPFs for pesticides in a risk assessment.

4.2 Organophosphates

OPP included thirty-three chemicals in the organophosphate (OP) CMG. These chemicals were assessed for their environmental uses and potential exposure routes (oral, dermal, and inhalation). OPs were evaluated based on neurotoxicity. The common mechanism of toxicity is the inhibition of acetylcholinesterase via phosphorylation of acetylcholinesterase in the central nervous system (CNS) and the peripheral nervous system (PNS). As a matter of science policy, red blood cell cholinesterase data are considered an appropriate surrogate measure of CNS and PNS acetylcholinesterase activity and are often used as a measurement of potential effects (USEPA, 2002b). For OPs, toxicity studies in the rat provided the most extensive cholinesterase activity data for oral and inhalation routes and both sexes. The USEPA used rabbit studies for the dermal route for five chemicals because dermal toxicity data in rats were not available (USEPA, 2002b). The selections of RPFs were based on female rat brain cholinesterase studies for several reasons: 1) brain cholinesterase relative potency estimates are similar to red blood cell cholinesterase potency estimates, but have tighter confidence intervals 2) brain cholinesterase is a direct measure of the common mechanism of toxicity, and 3) females were found to be more sensitive than males to three OPs (there was equal sensitivity in the remaining thirty). Potency determinations for the oral route are based on the benchmark dose (BMD) where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected because this level is generally near the limit of sensitivity for determining statistically significant decreases in cholinesterase.

Methamidophos was chosen as the index chemical for OPs because it has a high quality database for the inhibition of acetylcholinesterase for the oral, dermal, and inhalation routes. Oral RPFs were calculated by dividing the BMD_{10} for methamidophos by the BMD_{10} of a given chemical in the CMG. The BMD is the preferred method for determining relative potency (USEPA, 2002b). However, unlike the database for oral toxicity, the database of OP dermal and inhalation studies with cholinesterase measurements is limited and a BMD_{10} cannot be derived for these exposure routes. Therefore, the potency for the dermal and inhalation routes was determined using comparative effect levels (CELs) for the inhibition of brain cholinesterase. The CEL is the dose that causes a minimum level of effect and does not involve modeling a dose-response curve. For OPs, the CEL was defined as the dose causing a maximum of 15% decrease in brain cholinesterase activity. The RPFs for the dermal and inhalation routes

of exposure were calculated using a CEL, as data for these routes was limited. Dermal and inhalation RPFs were calculated by dividing the CEL for methamidophos by the CEL for a given chemical in the CMG (USEPA, 2002b). Oral RPFs for OPs can be found in Table 5.

4.3 N-Methyl Carbamates

Within the carbamate pesticides there are three distinct subgroups: N-methyl carbamates, thiocarbamates, and dithiocarbamates (USEPA, 2001b). These subgroups were evaluated separately. Thirteen N-methyl carbamates (NMCs) were assigned to the same CMG based on similar structural characteristics and a common mechanism of action. These chemicals were assessed for all potential exposure routes (oral, dermal, inhalation).

NMCs were evaluated based on neurotoxicity. The common mechanism of toxicity is the inhibition of acetylcholinesterase via carbamylation of the serine hydroxyl group located in the active site of the enzyme in the CNS and PNS. Toxicity studies included in the NMC database were male and female rat brain cholinesterase inhibition studies. Potency determinations are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). In cases where male and female rats provide similar BMD_{10} estimates, USEPA developed joint potency estimates (methomyl, pirimicarb, and thiodicarb). When male and female data produced statistically different results (aldicarb and carbaryl), the selections of RPFs were based on male rat studies, as males were found to have a lower BMD_{10} than females. Methiocarb and propoxur were based on male cholinesterase inhibition since they are the only data available. For n-methyl carbamates, $BMDs_{10}$ were calculated for all exposure routes. The calculation of route-specific BMDs is preferred over the use of CELs because it accounts for route-specific kinetics, which may influence potency. Oxamyl was chosen as the index chemical for oral, dermal, and inhalation RPFs since it had high quality dose-response data for all exposure routes. RPFs were calculated by dividing the BMD_{10} of oxamyl by the BMD_{10} of a given chemical in the CMG (USEPA, 2007). Oral RPFs for NMCs can be found in Table 6.

4.4 Thiocarbamates and Dithiocarbamates

On August 17, 2001, OPP assessed the thiocarbamates and dithiocarbamates for a common mechanism of toxicity. Six thiocarbamates were stated to belong to a CMG based on the potential to produce a common toxic effect (neuropathy of the sciatic nerve) and the similarities in metabolism, particularly to a reactive sulfoxide intermediate. RPFs were calculated based on comparing the no observed adverse effects levels (NOAELs) of each thiocarbamate due to the lack of robust dose-response data that would support a comparison of BMD_{10} values (USEPA, 2001a). In response to the assessment, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) commented there was insufficient evidence to support a common mechanism of toxicity and indicated a common metabolic product may not even exist. Therefore, on December 19, 2001, OPP produced a memorandum stating that the RPFs developed in the August 17, 2001 assessment are not appropriate for use for thiocarbamates as the evidence for a common mechanism and effect is not definitive (USEPA, 2001b). Currently, USEPA does not support the use of RPFs for thiocarbamates (USEPA, 2015).

Five dithiocarbamates (mancozeb, maneb, metiram, ziram, and thiram) were found to belong to a CMG based on the production of a common neurotoxic metabolite, carbon disulfide (USEPA, 2001c). No RPFs were calculated in this document. However, on December 19, 2001, OPP produced a memorandum stating that, based on the recommendations of the SAP and comments from the public, OPP re-evaluated the data and concluded that the available evidence does not support a common mechanism for neuropathology (USEPA, 2001d). Currently, USEPA does not support the use of RPFs for dithiocarbamates (USEPA, 2015).

4.5 Triazines

OPP included five triazines (atrazine, simazine, desethyl-s-atrazine, desisopropyl-s-atrazine, and diaminochlorotriazine) into the same CMG. Triazines were evaluated based on neuroendocrine effects. The common mechanism of toxicity involves the disruption of the hypothalamic-pituitary-gonadal axis. The hypothalamic-pituitary axis is involved in the development and maintenance of the reproductive system, bone formation, and immune, CNS, and cardiovascular functions. Therefore, disruption can lead to a variety of adverse health effects. Atrazine was chosen as the index chemical. Evaluation of endocrine-related data demonstrated potencies for chemicals in the CMG were equal or slightly less than atrazine. Therefore, an RPF of 1 was used for all chemicals in the CMG (USEPA, 2006a). Oral RPFs for triazines can be found in Table 7.

4.6 Pyrethrins and Pyrethroids

OPP included a total of 15 naturally occurring pyrethrins (including pyrethrins I and pyrethrins II) and synthetic pyrethroids that belong to the same CMG. The common mechanism grouping is based on 1) shared structural characteristics, 2) shared ability to interact with the voltage-gated sodium channels, which results in disruption of membrane excitability in the nervous system, and 3) neurotoxicity characterized by two different toxicity syndromes. OPP's CMG science policy paper (USEPA, 2011a) discusses how behavioral responses, particularly in the rat, can be used as sensitive indicators of pyrethroid toxicity. Rat behavior studies from Weiner et al. (2009) and Herberth (2010) were selected for benchmark dose modeling. A BMD_{20} was calculated based on a 20% change from controls. Behavioral data tends to have a higher level of variability compared to other biomarkers of toxicity. Due to the high variability and smaller sample size of the pyrethrin behavioral data, the BMD_{20} is the lowest dose for which a significant change can be detected from control values. It is consistent with the threshold used in other pyrethroid behavior studies (USEPA, 2011b). Deltamethrin was chosen as the index chemical because it has the most robust database of guideline and literature studies and is of sufficient quality to minimize error and uncertainty in cumulative risk assessments. Oral RPFs for pyrethrins and pyrethroids can be found in Table 8.

4.7 Chloroacetanilides

OPP included two pesticides (alachlor and acetochlor) in the same CMG. Both compounds produce nasal olfactory epithelium tumors in rats by a common mechanism including cytotoxicity of the olfactory epithelium, followed by regenerative cell proliferation of the nasal epithelium, and neoplasia if cytotoxicity and proliferation are sustained. Additionally, both compounds produce thyroid follicular cell tumors in rats by

UDPGT induction, increased TSH, alterations in T3/T4 hormone production, and thyroid hyperplasia (USEPA, 2006b). Because tumor development for these chemicals has a non-linear mode of action, tumor incidences were used to derive NOAELs for nasal tumors in male and female rats. Alachlor was chosen as the index chemical (USEPA, 2006b). The RPF was calculated using the ratio of the NOAEL for alachlor to the NOAEL for acetochlor. The oral RPF for acetochlor can be found in Table 9.

5. Application of Dose Additivity for Pesticides

As detailed in Section 2.1 (Dose Additivity), when multiple pesticides belonging to a CMG are found at a site, the individual concentrations of the pesticides are multiplied by their respective RPF values to get an ICED. All ICEDs are then summed to get the total ICED.

5.1 Which pesticides to include

Because pesticides are specialized for both the type of organism (insecticide versus herbicide) and the location of application (e.g., agricultural versus residential), colocation of pesticides within and among CMGs is not assumed. Pesticides are applied in many scenarios (application to food crops, use in residential and commercial buildings, and lawn care) over various spatial areas making predicting potential exposures difficult (USEPA, 2003). While assessment of human health risk is necessary when multiple chemicals from a CMG are present, the detection of one or more pesticides does not confirm or imply the presence of others. <u>The dose additivity approach should be used only for those pesticides that are detected at a site</u>. An example calculation is shown in Table 10.

5.2 Route specific RPFs

The TEFs for PCDDs/PCDFs, PCBs, and PAHs are intended to be applicable for all routes of exposure. For pesticides, USEPA made an attempt to develop route-specific RPFs. Thus, some pesticides have separate RPFs for oral, dermal, and inhalation routes of exposure, some have RPFs for two routes, while other pesticides have only oral route RPFs. The existence of route-specific RPFs, and their availability for some but not other pesticides, complicates their use in calculating risks and developing risk-based CTLs. One approach to include all RPFs when available would be to create a weighted RPF based upon the relative contribution of oral, dermal, and inhalation exposure to total exposure. This weighted RPF could be used with standard risk and CTL equations in the same way that calculations are performed for PCDDs/PCDFs, PCBs, and PAHs. However, the weighting would depend upon the specific exposure assumptions selected for the three routes and chemical/physical properties of the pesticide. Therefore, it would have to be derived for each chemical, exposure scenario, and with any site-specific deviations for default assumptions. This makes this approach cumbersome as a general method for implementing dose additivity for pesticides. Another approach would be to use different risk and CTL equations where oral, dermal, and inhalation risks are calculated separately, each with its own concentration term, and then summed. This would require a separate set of risk equations for pesticides, which may be confusing and difficult to implement as a general method. The simplest approach, which is recommended, is to create ICED values using the oral RPF [only] and use the standard equations for calculating risk and developing

risk-based CTLs. Generally, dermal and inhalation exposures for these chemicals from environmental media are low compared with oral exposure, and the error produced by using the oral RPF for all routes should be small. If there is a site-specific situation in which dermal or inhalation exposure is expected to be substantial relative to oral exposure, then either of the two other approaches discussed above can be used to more accurately estimate the contribution of these exposure routes to total risk.

5.3 Comparison with CTLs

Often the objective of evaluating dose-additivity is to determine whether the combined effects of the chemicals cause them to exceed a CTL. For the pesticides, this process is somewhat more complicated than for PCDDs/PCDFs, PCBs, and PAHs. The complication arises from the fact that the pesticides may have toxic effects that need to be addressed other than the effects that form the basis for the CMGs. A clear example is carcinogenicity. All of the CMGs are based upon non-cancer effects, while some of the pesticides in these CMGs are carcinogens. [A list of pesticides in the five CMGs that are carcinogens is shown in Table 11.] Consequently, in addition to additive non-cancer effects among the class of pesticides, potential carcinogenic effects also need to be addressed through comparison of concentrations of these pesticides with their individual CTLs derived based upon cancer risk. An example comparison can be found in Table 12. These CTLs appear in Chapter 62-777, FAC or are derived on a site-specific basis. With respect to non-cancer effects, some pesticides have non-cancer effects in addition to those reflected in their CMG. Consideration of these effects is also accomplished by comparing concentrations of the pesticides with their individual CTLs derived based upon non-cancer risk. Dose additivity should be evaluated separately by comparing the total ICED for the CMG with <u>a CTL for the index chemical derived specifically based upon the common toxic effect</u>. That CTL is based on a reference dose derived from the CMG analysis conducted by the USEPA, and may be different from the CTL based upon a reference dose from another source such as IRIS. To minimize confusion, a separate set of CTLs for the index chemicals appears in Chapter 62-777, FAC for the purpose of determining dose-additivity of pesticides.

For the purposes of cleanup under 62-780, F.A.C., a chemical must be addressed as part of the risk management strategy for the site if any of the applicable CTLs are exceeded.

References:

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Table 1. Toxic Equivalency Factors for PCDDs/PCDFs

Chemical	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
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

* Index chemical

Table 2. Example Calculation of Total TCDD Equivalents for Polychlorinated Dioxins and Furans

Polychlorinated dibenzodioxins				
Congener	Analytical Result (mg/kg)	Concentration (mg/kg)	TEFs	2,3,7,8-TCDD Equivalents (mg/kg)
2,3,7,8-TCDD	0.0000000062	0.0000000062	1	0.000000006
1,2,3,7,8-PeCDD	0.00000053 U	0.00000027	1	0.0000003
1,2,3,4,7,8-HxCDD	0.0000000042	0.0000000042	0.1	0.0000000004
1,2,3,6,7,8-HxCDD	0.00000088 U	0.00000044	0.1	0.00000004
1,2,3,7,8,9-HxCDD	0.0000000031	0.0000000031	0.1	0.0000000003
1,2,3,4,6,7,8-HpCDD	0.0000099 U	0.000005	0.01	0.00000005
OCDD	0.000068	0.000068	0.0003	0.00000002
			Total Dioxin Equivalents=	0.0000004

Polychlorinated dibenzofurans				
Congener	Analytical Result (mg/kg)	Concentration (mg/kg)	TEFs	2,3,7,8-TCDD Equivalents (mg/kg)
2,3,7,8-TCDF	0.0000072 U	0.0000036	0.1	0.0000004
1,2,3,7,8-PeCDF	0.00000094	0.00000094	0.03	0.00000003
2,3,4,7,8-PeCDF	0.0000046 U	0.0000023	0.3	0.0000007
1,2,3,4,7,8-HxCDF	0.000000089	0.000000089	0.1	0.000000009
1,2,3,6,7,8-HxCDF	0.0000055 U	0.0000028	0.1	0.0000003
1,2,3,7,8,9-HxCDF	0.00056 U	0.00028	0.1	0.000028
2,3,4,6,7,8-HxCDF	0.00000092	0.00000092	0.1	0.00000009
1,2,3,4,6,7,8-HpCDF	0.0000085	0.0000085	0.01	0.00000009
1,2,3,4,7,8,9-HpCDF	0.00000000066	0.0000000007	0.01	0.000000000007
OCDF	0.00000049 U	0.00000025	0.0003	0.00000000008
			Total Furan Equivalents =	0.000030

			Total TEQs; Dioxins + Furans=	0.0000304

Table 3. Toxic Equivalency Factors for PAHs

Chemical	TEF
Benzo(a)pyrene*	1
Benzo(a)anthracene	0.1
Benzo(b)fluoranthene	0.1
Benzo(k)fluoranthene	0.01
Chrysene	0.001
Dibenz(a,h)anthracene	1
Indeno(1,2,3-cd)pyrene	0.1

 * Index chemical

Table 4. Example Calculation of Total BaP Equivalents for Polycyclic Aromatic Hydrocarbons

Contaminant	Analytical Result (mg/kg)	Concentration (mg/kg)	TEFs	Benzo(a)pyrene Equivalents (mg/kg)
Benzo(a)pyrene	0.051	0.051	1.0	0.0510
Benzo(a)anthracene	0.25 U	0.125	0.1	0.0125
Benzo(b)fluoranthene	0.0012	0.0012	0.1	0.0001
Benzo(k)fluoranthene	0.89	0.89	0.01	0.0089
Chrysene	0.37	0.37	0.001	0.0004
Dibenz(a,h)anthracene	0.0064 U	0.0032	1.0	0.0032
Indeno(1,2,3-cd)pyrene	0.003 U	0.0015	0.1	0.0002

Total Benzo(a)pyrene Equivalents = 0.0762

(Note: For comparing to the soil direct exposure CTL in 62-777, the B(a)P equivalents are rounded to one decimal place. In the example above, the rounded result would be 0.1 mg/kg B(a)P TEQs.)

Table 5. Organophosphate Relative Potency Factors

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
Dichlorvos	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos*	**1.00**	**1.00**	**1.00**
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

* Index Chemical

Table 6. N-Methyl Carbamate Relative Potency Factors

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Aldicarb	4.00		
Aldicarb sulfone	3.44		
Aldicarb sulfoxide	3.68		
Carbaryl	0.15	0.71	0.51
Carbofuran	2.4		
3- and 5-Hydroxycarbofuran	2.4		
Formetanate HCL	2.18		
Methiocarb	0.18	0.09	0.62
Methomyl	0.67		
Oxamyl*	**1.00**	**1.00**	**1.00**
Pirimicarb	0.02		
Propoxur	0.11	0.03	0.18
Thiodicarb	0.89		

* Index chemical

Table 7. Triazine Relative Potency Factors

Chemical	Oral RPF
Atrazine*	**1**
Simazine	1
Desethyl-s-atrazine	1
Desisopropyl-s-atrazine	1
Diaminochlorotriazine	1

* Index chemical

Table 8. Pyrethroid (Including Pyrethrins) Relative Potency Factors

Chemical	Oral RPF
Allethrin	0.11
Bifenthrin	1.01
Cyfluthrin	1.15
Lambda-Cyhalothrin	1.63
Cyphenothrin	0.15
Cypermethrin	0.19
Deltamethrin*	**1.00**
Esfenvalerate	0.36
Fenpropathrin	0.50
Tau-Fluvalinate	1.00
Imiprothrin	0.02
Permethrin	0.09
Prallethrin	0.10
Pyrethrins	0.02
Resmethrin	0.05

* Index chemical

Table 9. Chloroacetanilide Relative Potency Factors

Chemical	Oral RPF
Alachlor*	**1.00**
Acetochlor	0.05

* Index chemical

Table 10. Example Calculation of Total Oxamyl Equivalents for N-Methyl Carbamates
(Note that only detected pesticides are included in the calculation)

N-Methyl Carbamates				
Pesticide	Analytical Result (mg/kg)	Concentration (mg/kg)	Oral RPF	Oxamyl Equivalents (mg/kg)
Aldicarb	56	56	4	224
Aldicarb sulfone	150	150	3.44	516
Aldicarb sulfoxide	33	33	3.68	121
Carbaryl	87 U		0.15	
Carbofuran	41 U		2.4	
3- and 5-Hydroxycarbofuran	5 U		2.4	
Formetanate HCL	11 U		2.18	
Methiocarb	320	320	0.18	58
Methomyl	68	68	0.67	46
Oxamyl	460	460	1	460
Pirimicarb	15 U		0.02	
Propoxur	78	78	0.11	8.6
Thiodicarb	32 U		0.89	
			Total Oxamyl Equivalents=	1434

Table 11. Carcinogenic Pesticides

Chemical*
Acephate
Alachlor
Atrazine
Dichlorvos
Ethoprop
Permethrin
Resmethrin
Simazine
Tetrachlorvinphos

*Carbaryl, pirimicarb, propoxur, and thiodicarb are also classified as probable carcinogens or likely to be carcinogenic but were not included in this list because no cancer slope factors or inhalation unit risks exist for these pesticides. As such, a CTL based on a cancer endpoint cannot be calculated.

Table 12. Example SCTL comparison for a pesticide (acephate) which has both non-cancer and cancer effects

Pesticide	Analytical Result (mg/kg)	Oral RPF	Methamidophos equivalents	Methamidophos residential SCTL based on non-cancer effects (Ch. 62-777, F.A.C, 2005)	Exceeds non-cancer SCTL?
Acephate	50	0.08	4.0	3.1	Yes

Pesticide	Analytical Result (mg/kg)	Acephate residential SCTL based on cancer effects (mg/kg) (Ch. 62-777, F.A.C, 2005)	Exceeds cancer SCTL?
Acephate	50	120	No

Acephate is a member of the organophosphate CMG. The basis for grouping the organophosphates together is shared neurotoxic non-carcinogenic effects. Thus, when acephate is present at a contaminated site, it should be evaluated for its non-carcinogenic effects, i.e. concentrations of acephate should be converted to methamidophos equivalents, as in the first table above. If any other pesticide in the organophosphate CMG is present, they too should be converted to methamidophos equivalents and added together to get the total ICED (see Table 10 for example calculation). The ICED should then be compared to the SCTL for the index chemical when the SCTL is derived for the same target effect (e.g. neurotoxicity). In this example, acephate is the only organophosphate present at the site; therefore, the analytical result is converted to methamidophos equivalents, which can then be directly compared to the residential SCTL derived to be protective of methamidophos effects of neurotoxicity. In this example, the acephate is in exceedance of the methamidophos residential SCTL.

However, acephate is known to also produce carcinogenic effects. To assess the cancer risk from acephate, concentrations at a site should be directly compared to the acephate residential SCTL derived to be protective of carcinogenic effects. In this example, the analytical result falls below the acephate residential SCTL for cancer effects.

For the purposes of cleanup under 62-780, acephate would need to be addressed as a chemical of concern because the total methamidophos equivalents exceed the methamidophos SCTL based on non-cancer effects.