Pesticide Science Policy

STANDARD OPERATING PROCEDURE (SOP) FOR INCORPORATING SCREENING-LEVEL ESTIMATES OF DRINKING WATER EXPOSURE INTO AGGREGATE RISK ASSESSMENTS

PUBLIC COMMENT DRAFT
September 1, 2000

Office of Pesticide Programs
Environmental Protection Agency

EXECUTIVE SUMMARY

This document is the Standard Operating Procedure (SOP) which provides a step-by-step process for staff to follow when incorporating screening-level estimates of drinking water exposure into the Office of Pesticide Program's (OPP) human health aggregate risk assessments. It contains: 1) terms, definitions, descriptions, and calculations for use in incorporating estimates of pesticide concentrations in surface water and groundwater from screening-level models into aggregate risk assessments, 2) examples of specific language that may be used in health effects risk assessment documents to characterize screening-level exposure estimates for drinking water, and 3) an appendix containing example scenarios and calculations. This document provides the detailed procedures for implementing OPP's overall policy as articulated in "Estimating the Drinking Water Component of a Dietary Exposure Assessment" (See 64 FR 61346-61348, November 10, 1999).

Under the procedures outlined in this document, the resulting estimates of exposure associated with a pesticide in drinking water are considered to be unrefined, high-end, upper-bound values. However, since many compounds can be "cleared" of drinking water concerns using these screening-level procedures, the process saves limited resources by providing an efficient means to determine whether a more refined assessment of drinking water exposure for a specific compound is warranted. This document is an updated version of the existing SOP for incorporating drinking water exposure into aggregate risk assessment and replaces the previous SOP dated August 1, 1999 (HED SOP 99.5, 1999). For additional information regarding the drinking water exposure models which OPP's Environmental Fate and Effects Division uses to provide the exposure estimates used in this SOP, refer to the following document: "Drinking Water Screening Level Assessment, Part A: Guidance for Use of the Index Reservoir in Drinking Water Exposure Assessments, Part B: Applying a Percent Crop Area Adjustment to Tier 2 Surface Water Model Estimates for Pesticide Drinking Water Exposure Assessments."

Standard Operating Procedure (SOP) for Incorporating Screening-Level Estimates of Drinking Water Exposure into Aggregate Risk Assessments

Introduction

This document provides guidance in the form of a standard operating procedure (SOP) for incorporating screening-level estimates of exposure to pesticides in drinking water into the OPP's aggregate human health risk assessments. It outlines the step-by-step process the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) have developed to date to coordinate the necessary interactions between the two divisions. It describes in detail the processes outlined in the OPP's policy on estimating exposures to pesticides in drinking water[1].

This SOP describes a generic process for any of the various actions generated in the Registration Division (RD) and the Special Review and Reregistration Division (SRRD), including reregistration eligibility decisions (REDs), the application for registration of new chemicals and new/amended uses, and emergency exemptions (Section 18s). The SOP also includes specific examples of language to be used in the following situations: 1) when a risk assessment is not warranted because of the use pattern or chemical characteristics of the pesticide, and 2) when screening-level models' estimates do not exceed drinking water levels of comparison. All such language is set in italicized typeface and indented. The SOP will evolve over time as HED and EFED refine their screening-level process for assessing exposure to pesticide residues in drinking water.

To assess whether drinking water exposures could potentially contribute significantly to aggregate risk, the OPP uses an approach that incorporates a series of tiers, or screening procedures. OPP's tiered approach provides an efficient process for determining which pesticides warrant a more detailed assessment of drinking water exposures. Progression through the tiers is expected to result in progressively more accurate and realistic estimates of pesticide concentrations in drinking water. This document describes the initial tiers of OPP's current screening-level assessment process. The screening-level process assures that any potential drinking water exposure will not result in unacceptable levels of aggregate risk. The goal of this process is to identify pesticides for which there is no reason to suspect that drinking water exposure will contribute significantly to aggregate risk.

The goal is reached by using estimates of exposure that are conservative enough that there is little possibility that they will be significantly exceeded for anyone in the population. If there does appear to be a possibility of unacceptable exposure, a more detailed and quantitative assessment of aggregate exposure may be warranted on a case-by-case basis. However, if aggregate risk based on conservative estimates of exposure under the screening-level process are below the level of concern, there is no need to conduct a more refined exposure assessment for drinking water, and resources are conserved.

This approach requires that the drinking water exposure assessment address two questions: 1) For

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[1] **USEPA, "Estimating the Drinking Water Component of a Dietary Exposure Assessment," 64 FR 61346-61348, November 10, 1999.**

what concentration of a pesticide in drinking water can OPP be confident that there is no one in the exposed population receiving drinking water with the pesticide at a significantly higher concentration, and 2) Is that a concentration that may cause concern in light of aggregate exposure? Any estimate of drinking water exposure developed under this screening-level paradigm represents an upper bound and should be characterized as such in the risk assessment.

In this approach, the resulting drinking water exposure provided to the risk manager does not represent an accurate estimate of drinking water exposures for most of the population, although it might be representative for some maximally exposed individual. The risk manager can be confident that the resulting assessment will yield overestimates of risk. Procedures for a more quantitative estimate of exposure to pesticides in drinking water yielding more accurate estimates of risk will be the subject of a different paper.

EFED's prime responsibility in this screening-level process is to develop screening-level estimates of pesticide (and significant degradation products) concentrations in ground and surface water for comparison to a theoretical limit for the pesticide in drinking water. All such concentration estimates are considered to be high end or upper bound estimates for the purposes of comparison to drinking water limits. Basic environmental fate and transport data, e.g., a description of the pesticide's (and degradation products') persistence and mobility should accompany the concentration estimates. If an estimation is not possible, EFED provides a complete explanation regarding deficiencies in the fate and transport data which preclude generation of a model estimate.

HED uses the screening-level estimates of pesticide concentrations in ground and surface water sources to develop a screening-level drinking water exposure assessment that will be incorporated into the overall risk assessment. The drinking water assessment process is an iterative process between HED and EFED, where HED drives refinement of the estimates through an on-going risk assessment process. If necessary, HED will refine its exposure and risk assessment from residues in food to include anticipated residues (using percent of crop-treated information, monitoring and field trial data, and probabilistic assessments where appropriate) before requesting refinements to estimated pesticide concentrations in water from EFED.

Step 1: Initial Meetings for REDs or New Chemicals.

! Reregistration Eligibility Decisions (REDs)

For newly assigned REDs, it is suggested that SRRD initiate a meeting with members of HED, EFED, and the Biological and Economic Analysis Division (BEAD) who have been assigned responsibility for their divisions' RED chapter. This meeting would introduce the responsible staff members from each division to one another and provide for discussing specific time-lines regarding drinking water assessments. In addition, use patterns, toxicity issues, degradation products/metabolite issues, and any other major issues affecting the risk assessment could be discussed. SRRD sends a formal request (bean sheet) to EFED for pesticide concentration estimates in surface and ground water.

For REDs in process, SRRD sends a bean sheet to EFED requesting pesticide concentration estimates in surface and ground water. Where an initial meeting has not been held, HED and EFED need to be proactive and take responsibility for coordinating their RED activities. In general, HED staff will contact the appropriate EFED staff to initiate information exchange relevant to the risk assessment for drinking water. SRRD/HED staff in the interdisciplinary reregistration branches will take responsibility for keeping EFED staff informed of HED's scheduled due dates for RED chapters, presentation dates of their risk assessments to the Science Assessment Review Committees (SARCs), and setting up additional follow-up meetings with EFED to discuss drinking water exposure assessments for REDs assigned to them.

Time Frame: ASAP after chemical assignments have been made.

! New Chemicals

It is suggested that RD initiate a meeting after data review packages are sent to HED and EFED for review and after HED and EFED assign team members to the new chemical. The purpose of the meeting is to introduce HED and EFED team members to one another and to consider the uses associated with the new chemical, and to discuss timelines for the drinking water assessments. RD should provide any important use and label information to HED and EFED as soon as possible. RD sends a bean sheet to EFED for pesticide concentration estimates in drinking water. RD/HED staff in the interdisciplinary registration branches will take responsibility for keeping EFED staff informed of HED's scheduled due dates for risk assessment documents, presentation of their risk assessments to SARCs, and setting up additional follow-up meetings with EFED to discuss drinking water exposure assessments for new chemicals assigned to them.

Time Frame: ASAP after new chemical assignments have been made.

! Emergency Exemptions - Section 18s

RD sends a bean sheet simultaneously to HED and EFED for the Section 18 action. RD coordinates the due dates for EFED's assessment with HED's due date so that HED has time to incorporate EFED's information into their risk assessment, i.e., EFED's memo must be sent to HED a few days prior to HED's due date. EFED sends their finished assessment directly to HED

and sends one copy to RD to close out the action. Under the Food Quality Protection Act (FQPA), all uses of the chemical may need to be considered, not just the emergency exemption use.

! Other Actions

RD uses the same general process, as described above for new chemicals, for new and amended uses, and time-limited tolerances. However, under the FQPA, all uses of the chemical may need to be considered, not just the new/amended use or the time-limited tolerance.

Step 2: HED Invites EFED to Metabolism Assessment Review Committee (MARC) Meetings (All Actions)

! HED takes responsibility for inviting EFED to the HED Metabolism Assessment Review Committee (MARC) meeting where a decision is made to include or exclude the soil/water degradation products in the tolerance expression or risk assessment. During the MARC meeting plant/livestock metabolites are compared with soil/water degradation products. The MARC determines whether soil/water degradation products are of toxicological concern and present in significant concentrations to warrant inclusion into the drinking water exposure assessment. EFED should provide a comprehensive fate profile of the degradation products including their chemical identification, patterns of formation and decline in terrestrial and aquatic environments, and relative concentrations and mobility in soil and water. HED informs SRRD/RD of any issues relating to soil/water degradation products that may impact the human health risk assessment.

! As soon as possible, HED staff provide the EFED staff with as much information as is available on the selected toxicity endpoints. This will enable EFED and HED to discuss toxicity endpoints relative to available exposure numbers early in the process. This can be done during the MARC meetings.

Step 3: Determine if a Drinking Water Exposure Assessment is Needed

! A drinking water exposure assessment *is not always needed*. **For instance, if the use pattern associated with the action meets the following conditions**:

--Active registrations exist for only the following types of uses: baits, greenhouse uses, seed treatments, potato seed piece treatments, crack and crevice treatments, food handling establishment uses, other indoor uses, or uses related to import tolerances only -- EFED states this in a brief memo to HED and completes the bean sheet associated with the initial request for drinking water concentration estimates. HED makes a statement such as the following in the risk assessment document:

"OPP has considered the registered uses and the available data on persistence and mobility for [chemical]. OPP has determined through a

qualitative assessment that the use pattern associated with [chemical] [specify use pattern parenthetically] is not expected to impact water resources through labeled uses. In light of this finding, OPP believes that [chemical] use will not impact ground water or surface water resources, and therefore is not expected to lead to exposure to humans through drinking water. If new uses are added in the future, OPP will reassess the potential impacts of [chemical] on drinking water as a part of the aggregate risk assessment process."

AND/OR

-- EFED determines that the pesticide and its toxicologically significant degradation products are neither persistent nor mobile and there is clearly no concern regarding the impact of the pesticide's use on drinking water. In this case, EFED states this in a brief memo to HED, which includes a brief description of the chemical's (and its toxicologically significant degradation products) persistence and mobility characteristics, and completes the bean sheet associated with the initial request for drinking water concentration estimates. HED makes a statement such as the following in the risk assessment document:

"OPP has considered the registered uses and the available data on persistence and mobility for [chemical(s)]. OPP has determined through a qualitative risk assessment that the physical and chemical characteristics of [chemical(s)] are such that they are not expected to impact water resources. [Chemical(s)] is/are neither persistent nor mobile. [Place persistence and mobility characteristics here.] In light of these findings, OPP believes that [chemical] use will not impact ground water or surface water resources, and, therefore, is not expected to lead to exposure to humans through drinking water. If new uses are added in the future, OPP will reassess the potential impacts of [chemical] on drinking water as a part of the aggregate risk assessment process."

! **A drinking water exposure and risk assessment** *is usually needed* **if the pesticide is expected or known to impact water resources based on usage pattern, persistence and mobility criteria, or monitoring data, and thereby could result in exposure through drinking water.**

Step 4: EFED Provides Screening-Level Estimates of Pesticide Concentrations in Drinking Water from Surface and Ground Water to HED

- **Once it has been determined that a drinking water exposure assessment is needed, EFED provides screening-level estimates of the pesticide's concentration in drinking water from surface and ground water, and a brief description of the chemical's persistence and mobility to HED. If any degradation products were included in the risk assessment as a result of the MARC meeting, screening-level estimates for those degradation products and their persistence and mobility should also be included. HED needs estimates of the maximum (peak), average annual, and multi-year mean concentration values for a pesticide for use in acute and chronic exposure assessments. EFED provides the requested estimates and persistence and mobility information in a memo to HED and completes the bean sheet associated with the initial request for drinking water estimates. EFED copies the memo to RD/SRRD.**

- **To provide HED with the required estimates, EFED initially conducts a screening-level assessment using tier 1 computer simulation models: Generic Estimated Environmental Concentrations (GENEEC) or First Index Reservoir Screening Tool (FIRST) for surface water estimates, and Screening Concentration In Groundwater (SCI-GROW) for groundwater estimates[2]. EFED's screening-level assessments with GENEEC or FIRST and SCI-GROW use the highest labeled application rate for a pesticide to provide estimates of the pesticide's concentrations in surface and ground water, respectively. These concentration estimates are considered to be upper bound for comparison to theoretical concentration limits for the pesticide in drinking water (discussed in Step 5), and considered adequate for screening-level purposes. From GENEEC, EFED provides a maximum concentration value, and the 56-day average concentration value to HED. From FIRST, EFED provides a maximum concentration value, and an average annual concentration value to HED. Concentration estimates from GENEEC or FIRST are used for the surface water exposure assessments. From SCI-GROW, EFED provides a single concentration value (a 90-day average) to be used for groundwater assessments. Because residues of pesticides in groundwater do not fluctuate as widely over time as they do in surface water, one value is considered adequate for screening-level assessments. Adequate data for a screening-level assessment include all or most of the following: application rates, data on the soil and water degradation products, solubility, soil-water adsorption coefficients, and rates of decay associated with hydrolysis, soil/water photolysis, and aerobic/anaerobic soil and water degradation processes.**

- **In general, in a screening-level assessment for surface water, EFED will use a tier 1 model (GENEEC or FIRST) before using a tier 2 surface water model: Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS). The GENEEC and FIRST models are subsets of the PRZM/EXAMS model that use a specific high-end runoff scenario for pesticides. GENEEC incorporates a pond farm scenario, while both FIRST and PRZM/EXAMS incorporate an index reservoir environment in place of the previous farm pond scenario. The tier 2 PRZM/EXAMS model includes a percent crop area (PCA) factor as an adjustment to account for the maximum percent crop coverage within a**

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[2] **Currently, OPP uses GENEEC as the tier 1 screening-level model for surface water-sourced drinking water assessments. OPP expects to replace GENEEC with FIRST as the tier 1 screening-level model for surface water-sourced drinking water assessments in the future.**

watershed or drainage basin defined as an eight-digit Hydrologic Unit Code (HUC). Specific PCAs have been developed for some crops. For all other crops, a default PCA of 0.87 has been recommended. The default PCA represents the highest percentage of land within an eight-digit HUC in agricultural production, but is not specific to a particular crop (Effland, et al., 1999).

- **As a part of a screening-level assessment, EFED also briefly considers available monitoring data from any of a variety of sources. These can include USEPA's STORET and National Pesticide Survey databases, USGS' National Water Quality Assessment Program (NAWQA) data, the Pesticides in Groundwater Database, data collected under the Safe Drinking Water Act (SDWA), state monitoring programs, small-scale prospective groundwater studies, and runoff studies. Results from the monitoring studies are compared to the model estimates to ensure that the models are not underestimating a chemical's potential concentrations in surface and ground waters.** Once EFED has verified that the model estimates do not underestimate concentrations reported in ground and surface waters from monitoring data, EFED provides the concentration estimates to HED.

- If all or a geographic subset of the monitoring data consistently exceed the model values, EFED conducts an in-depth review of the monitoring data and disregards the model estimates. EFED provides a comparison of the monitoring data to the model values. If the monitoring data are judged to be reliable and appropriate for a drinking water assessment, HED uses these data to prepare the required exposure and risk assessments. (See Step 10).

Step 5: Using Drinking Water Levels of Comparison Values (DWLOCs) in a Screening-Level Exposure Assessment for Drinking Water

What is a DWLOC?

HED uses Drinking Water Level of Comparison (DWLOCs) values as a surrogate measure of exposure and risk. The models currently used to estimate pesticide concentrations in drinking water are very conservative and used as screening tools in the risk assessment process. HED does not use concentration estimates from current models (GENEEC, FIRST, PRZM/EXAMS, and SCI-GROW) to quantify risk as a percentage of the reference dose (%RfD) or population adjusted dose (%PAD). [The PAD is the RfD after adjustment by a FQPA safety factor **and can be considered the target exposure not to be exceeded for a given pesticide.] Instead, HED compares the model estimates to DWLOC values. This comparison provides a semi-quantitative risk assessment for drinking water until the drinking water exposure estimates can be refined.**

In calculating a DWLOC, HED determines how much of the acceptable exposure (i.e., the RfD or PAD) is available for exposure through drinking water. Simply, if 10 mg/kg/day is the chronic RfD or PAD, and chronic exposure through average food residues is 6 mg/kg/day, and there are no residential uses, or other exposures, then 4 mg/kg/day is "allowed" or "available" for exposure through drinking water. This allowable exposure through drinking water is used to calculate a

concentration that is considered a *theoretical* limit for the pesticide in drinking water. The DWLOC takes into account estimates of aggregate exposure to a pesticide through food and home uses. It is considered a theoretical limit because the calculation uses default assumptions about body weight and drinking water consumption, and there is some uncertainty associated with the estimates of exposure from food and home uses. The body weights and consumption rates used are the standard default values used by the Office of Ground Water and Drinking Water in calculating drinking water standards (US EPA, OGWDW, 1989)[3].

How many DWLOCs are calculated?

Generally, a DWLOC will need to be calculated for each type of risk assessment required: acute, short-term, intermediate-term, chronic, and cancer. This could require calculations for: $DWLOC_{ACUTE}$, $DWLOC_{SHORT\text{-}TERM}$, $DWLOC_{INTERMEDIATE\text{-}TERM}$, $DWLOC_{CHRONIC}$, and $DWLOC_{CANCER}$.

Under each type of required risk assessment, DWLOCs should be calculated for the following populations in the Dietary Exposure Estimate Model (DEEM) using the assumed default values for body weight and consumption as noted:

U.S. Population/48 states <u>or</u> highest exposed adult male subgroup (70 kg body weight and 2 liters/day consumption)
Females* (60 kg body weight and 2 liters/day consumption)
Infants* (10 kg body weight and 1 liter/day consumption)
Children* (10 kg body weight and 1 liter/day consumption)

*** In the case of females, infants, and children, DEEM provides the exposure from food for various population subgroups. There are four subgroups for females listed in the standard DEEM analysis (13+ pregnant, 13+ nursing, 13-19 not pregnant or nursing, 20+ not pregnant or nursing). There are also four subgroups for infants and children. In these instances, the DEEM subgroup with the highest food exposure should be used when calculating the DWLOC specific to that population.**

For example, DEEM provides the following results for four subgroups of the female population:

Population Subgroup	**Exposure**
Females (13+ years, pregnant)	**0.000126**
Females (13+ years, nursing)	**0.000161**
Females (13-19 years, not pregnant or nursing)	**0.000157**
Females (20 years, not pregnant or nursing)	**0.000120**

[3] OPP acknowledges that there are differences in body weights and consumption across population subgroups, and although OPP does not consider them in the initial tiers of our screening-level process for estimating drinking water exposure as described in this document, these differences are real, and OPP will be taking them into account in subsequent refinements to the screening-level process. OPP will be using records containing **covariant data linking individual drinking water consumption and body weights for specific individuals within population subgroups as defined in the dietary exposure program (DEEM). Additional refinements to the screening process will be the subject of another document on quantitative procedures to assess exposure to pesticides in drinking water.**

In the example above, a DWLOC representing the population "females" should be calculated for "females 13+ years, nursing" since this is the subgroup for the female population with the highest exposure. In addition, if any of the subgroups for adult males is higher than the exposure of the general U.S. population, a DWLOC for the adult subgroup with the highest exposure should also be calculated. Typically, then, a different DWLOC for each of 4 populations will be calculated: U.S. population, females (the highest exposed subgroup within this population), infants and children (the highest exposed subgroups within these populations), and the highest exposed adult subgroup if any subgroup has an exposure that is greater than that for the U.S. population.

It should be noted that in some cases, a specific risk assessment is required for one specified population subgroup only. For example, for a chemical, an acute risk assessment is required only for females 13+ because the endpoint selected as the basis of the acute risk assessment is developmental toxicity. In this case, a $DWLOC_{ACUTE}$ should be calculated for the specific population subgroup for which the risk assessment is required, i.e., females 13+. No other DWLOC calculations for the acute risk assessment would be necessary. Generally, the population subgroups of interest for any required risk assessment are clearly stated in the Hazard Identification Assessment Review Committee (HIARC) document.

[Note: the RfD or PAD may be different for different populations. For example, a FQPA safety factor of 10X may be applied to females 13+ only for the acute dietary risk assessment. In this case, the appropriate PAD reflecting the additional 10X safety factor must be carried through the $DWLOC_{ACUTE}$ calculations for this population only.]

Step 6: Calculating Drinking Water Level of Comparison (DWLOCs) Values.

In general, the $DWLOC_{ACUTE}$ is the concentration in drinking water as a part of the aggregate acute exposure that occupies no more than 100% of the acute RfD or PAD. The $DWLOC_{CHRONIC}$ is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic RfD or PAD. The $DWLOC_{CANCER}$ is the concentration in drinking water as a part of the aggregate chronic exposure that results in a negligible cancer risk. Currently default daily consumption and body weight values (as used by the Office of Ground Water and Drinking Water) are used to calculate DWLOCs: 2L/70 kg (for adult males), 2L/60 kg (for adult females), and 1L/10 kg (for infants and children). For aggregate risk assessments that include short- and intermediate-term residential exposures, it may be necessary to calculate values for the $DWLOC_{SHORT-TERM}$ and the $DWLOC_{INTERMEDIATE-TERM}$. The necessary calculations are discussed later in this step. The necessary calculations for each type of risk assessment follow:

Acute Risk Assessment

- **The DWLOC for acute risk, is calculated as given in the equation below. It is assumed that the acute RfD or PAD are known for an acute dietary risk assessment, that the acute food exposures (at the 95th percentile of exposure for deterministic assessments or at the 99.9th percentile of exposure for probabilistic assessments) from an acute DEEM run are known, and that there is no residential exposure. Use default body weight and consumption rates, accordingly.**

$$DWLOCacute\ (ug/L) = \frac{[one\text{-}day\ water\ exposure\ (mg/kg\ bw/day)\ x\ body\ weight\ (kg)]}{[water\ consumption\ (L/day)\ x\ 10^{-3}\ mg/ug]}$$

$$one\text{-}day\ water\ exposure\ (mg/kg\ bw/day) = [AcutePAD - (one\text{-}day)\ food\ exposure\ (mg/kg\ bw/day)\ ]$$

Chronic Risk Assessment

! **The DWLOC for chronic risk is calculated as given in the equation below. It is assumed that the chronic RfD or PAD, and chronic food and residential (if any) exposures are known. Where chronic residential exposure is expressed as the average daily dose (ADD). Use default body weight and consumption rates, accordingly.**

$$DWLOC_{chronic}(ug/L) = \frac{chronic\ water\ exposure\ (mg/kg\ bw/day)\ x\ body\ weight\ (kg)}{water\ consumption\ (L/day)\ x\ 10\text{-}3\ mg/ug}$$

$$chronic\ water\ exposure\ (mg/kg/day) = [Chronic\ PAD - (average\ food + chronic\ residential\ exposure\ (ADD))\ (mg/kg/day)]$$

Cancer Risk Assessment

! **To calculate DWLOC for cancer risk, (assuming the MOE or q*, and chronic food and residential (if any) exposures are known),**

(A) If the risk is quantified using the *MOE approach*, calculate $DWLOC_{cancer}$ as above under acute risk, except include the chronic food and residential exposures in the aggregate exposure term when calculating the water exposure value.

[NOAEL/MOE (mg/kg/day)] - ([chronic food + chronic residential exposure (ADD)) (mg/kg/day)] = chronic water exposure (mg/kg/day)

(B) If the risk is quantified using a *q* approach*, where chronic residential exposure is expressed as the LADD or lifetime average daily dose. Generally, a $DWLOC_{CANCER}$ based on a q* is calculated for the US population only[4].

$$DWLOCcancer\ (ug/L) = \frac{[chronic\ water\ exposure\ (mg/kg\ bw/day)\ x\ body\ weight\ (kg)]}{[water\ consumption\ (L/day)\ x\ 10^{-3}\ mg/ug]}$$

$$chronic\ water\ exposure\ (mg/kg/day) = \frac{Negligible\ risk}{Q^*} - [(average\ food + chronic*\ residential\ exposure\ (LADD))\ (mg/kg/day)]$$

Short- and Intermediate - Term Risk Assessments

As a part of aggregate risk assessment, short-term and intermediate-term risk assessments requiring the incorporation of drinking water exposure and the calculation of DWLOC values, can be handled either through:

1) the reciprocal MOE equation ("1/MOE approach") for calculating an aggregate MOE and solving for the term MOE_{water}, or

2) the Aggregate Risk Index (ARI) method.

The reciprocal MOE equation using the 1/MOE approach can be used only if the acceptable MOEs are identical for all routes of exposure included in the calculation, otherwise, use the ARI method. Examples of DWLOC calculations using both methods are given in Appendix I.

Use the following guidance taken directly from the "Guidance for Performing Aggregate Exposure and Risk Assessments" when incorporating screening-level estimates of short- and intermediate-term drinking water exposure into aggregate risk assessments[5].

> **"Since short- and intermediate-term, single-source risk assessments are typically only done for worker and residential assessments, oral endpoints may not always be selected. If an**

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[4] OPP acknowledges that the current cancer risk assessment process does not consider estimates of less-than-lifetime exposures that may be warranted to cover early life effects. However, as cancer exposure assessment policy develops, future exposure assessments may include consideration of cancer risk for other population subgroups.

[5] US EPA, "Guidance for Performing Aggregate Exposure and Risk Assessments," 64 FR 61343-61346, November 10, 1999.

endpoint and NOAEL from an oral study are selected for either short- or intermediate-term dermal or inhalation risk assessment, this oral NOAEL and endpoint should be used to calculate the non-dietary, inadvertent hand-to-mouth exposure and the dietary (food and water) exposure components of the aggregate risk assessment. If an oral endpoint is needed for short- or intermediate-term assessment, yet only dermal and or inhalation endpoints have been selected for these assessments, the following default rules apply:

1) If an oral endpoint is needed for short term risk assessment for incorporation of dietary (food or water), or oral hand-to-mouth-type (non-dietary, inadvertent) exposures into aggregate assessment, and only dermal and/or inhalation endpoints have been selected, the acute oral endpoint (basis of the acute RfD or PAD) should be used to incorporate the oral component into the aggregate risk.

2) If an oral endpoint is needed for intermediate term risk assessment for incorporation of dietary (food or water), or oral hand-to-mouth-type (non-dietary, inadvertent) exposures into aggregate assessment, and only dermal and/or inhalation endpoints have been selected, the chronic oral endpoint (basis of the chronic RfD or PAD) should be used to incorporate the oral component into the aggregate risk."

Short-Term Risk Assessment Using the Reciprocal MOE Method

Whenever a short-term risk assessment is required for a pesticide with residential uses and the acceptable Margins of Exposure (MOEs) are identical for all MOEs in the calculation, the following equations should be solved for the term "MOE_{WATER},". The acceptable MOE is the product of the selected uncertainty factors (UFs) for the short-term risk assessment.

$$\text{Aggregate MOE} = \frac{1}{\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{WATER}} + \frac{1}{MOE_{ORAL}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}}}$$

$$MOE_{WATER} = \frac{1}{\frac{1}{MOE_{AGG}} - \left[\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}} + \frac{1}{MOE_{ORAL}}\right]}$$

Where the aggregate MOE_{AGG} is equal to the acceptable MOE for the short-term risk assessment:

the MOE_{FOOD} is based on the dietary exposure from average food residues (chronic exposure) compared to the short-term oral NOAEL or the acute dietary NOAEL,

the MOE_{WATER} is based on "allowable short-term water exposure" from average drinking water residues compared to the short-term oral NOAEL or the acute dietary NOAEL,

the MOE_{ORAL} is based on the calculated short-term oral hand-to-mouth residential exposures compared to the short-term oral NOAEL or the acute dietary NOAEL,

the MOE_{DERMAL} is based on the calculated short-term residential dermal exposures compared to the NOAEL selected for short-term dermal exposures,

and the $MOE_{INHALATION}$ is based on the calculated short-term residential inhalation exposures compared to the inhalation NOAEL (any time period).

After calculating the value for the term "MOE_{WATER}", solve the following equation for the allowable short-term water exposure, calculated as follows:

$$MOE_{WATER} = \frac{\text{Short-term oral or acute dietary NOAEL}}{\text{Allowable Short-Term Water Exposure}}$$

$$\text{Allowable Short-Term Water Exposure} = \frac{\text{Allowable short-term oral or acute dietary NOAEL}}{MOE_{WATER}}$$

Using the Allowable Short-Term Water Exposure value, the Short-term DWLOC is calculated as follows using the appropriate default values for body weights and consumption rates:

$$DWLOC_{SHORT\text{-}TERM}(\mu g/L) = \frac{\text{Allowable Short-Term Water Exposure (mg/kg/day) x Body Wt (kg)}}{\text{(1E-3 mg/}\mu\text{g) x Daily Drinking Rate (L/day)}}$$

Intermediate-Term Risk Assessment Using the Reciprocal MOE Method

Whenever, an intermediate-term risk assessment is required for a pesticide with residential uses the following equations should be solved for the term "MOE_{WATER}":

$$\text{Aggregate MOE} = \frac{1}{\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{WATER}} + \frac{1}{MOE_{ORAL}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}}}$$

$$MOE_{WATER} = \frac{1}{\frac{1}{MOE_{AGG}} - \left[\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}} + \frac{1}{MOE_{ORAL}}\right]}$$

Where the aggregate MOE_{AGG} is equal to the acceptable MOE for the intermediate-term risk assessment:

the MOE_{FOOD} is based on the dietary exposure from average food residues (chronic dietary exposure) compared to the intermediate-term oral NOAEL or the chronic dietary NOAEL,

the MOE_{WATER} is based on "allowable intermediate-term water exposure" from average drinking water residues compared to the intermediate-term oral NOAEL or the chronic dietary NOAEL,

the MOE_{ORAL} is based on the calculated intermediate-term oral hand-to-mouth residential exposures compared to the intermediate-term oral NOAEL or the chronic dietary NOAEL,

the MOE_{DERMAL} is based on the calculated intermediate-term residential dermal exposures compared to the NOAEL selected for intermediate-term dermal exposures,

and the $MOE_{INHALATION}$ is based on the calculated intermediate-term residential inhalation exposures compared to the inhalation NOAEL (any time period).

After calculating the value for the term "MOE_{WATER}," the "allowable intermediate-term water exposure" is calculated as follows:

$$MOE_{WATER} = \frac{\text{Intermediate-term oral or chronic dietary NOAEL}}{\text{Allowable Intermediate-Term Water Exposure}}$$

$$\text{Allowable Intermediate-Term Water Exposure} = \frac{\text{Intermediate-term oral or chronic dietary NOAEL}}{MOE_{WATER}}$$

Using the Allowable Intermediate-Term Water Exposure value, the Intermediate-term DWLOC is calculated as follows using the appropriate default body weights and consumption rates:

$$DWLOC_{INTERMEDIATE\text{-}TERM}(\mu g/L) = \frac{\text{Allowable Intermediate -Term Water Exposure (mg/kg/day) x Body Wt (kg)}}{\text{(1E-3 mg/}\mu\text{g) x Daily Drinking Rate (L/day)}}$$

Short- and Intermediate-term Risk Assessments Using the ARI Method

When Short- and Intermediate-term risk assessments cannot be conducted with the reciprocal MOE method, the equations below for the ARI method can be used.

$$\text{Aggregate ARI} = \frac{1}{\frac{1}{ARI_{FOOD}} + \frac{1}{ARI_{WATER}} + \frac{1}{ARI_{ORAL}} + \frac{1}{ARI_{DERMAL}} + \frac{1}{ARI_{INHALATION}}}$$

$$ARI_{WATER} = \frac{1}{\frac{1}{ARI_{AGG}} - \left[\frac{1}{ARI_{FOOD}} + \frac{1}{ARI_{DERMAL}} + \frac{1}{ARI_{INHALATION}} + \frac{1}{ARI_{ORAL}}\right]}$$

Where ARI = [$MOE_{CALCULATED}$ (i.e., FOOD, WATER, DERMAL, INHALATION, ORAL) ÷ $MOE_{ACCEPTABLE}$].

Sample calculations using the reciprocal MOE and ARI methods are given in Appendix I.

Step 7: Comparing DWLOC Values to Concentration Estimates from Surface and Ground Water Screening-Level Models

In general, maximum (peak) concentration estimates from the tier 1 or 2 screening-level models for surface water (GENEEC, FIRST or PRZM/EXAMS) are compared only to acute DWLOC values for the acute portion of the aggregate risk assessment. All other DWLOC values (short-term, intermediate-term, chronic, and cancer) are compared to the long-term average concentration estimates from the models for the short- and intermediate-term, chronic, and cancer portions of the aggregate risk assessment.

Because GENEEC only provides a 56-day average value, and not a longer-term average value, (i.e., an annual average or multi-year mean), the 56-day concentration value from GENEEC is divided by 3 for comparison to short-term, intermediate-term, chronic, and cancer DWLOC values. Because the groundwater model, SCI-GROW, only provides one concentration estimate (a 90-day average value), compare it to all DWLOC values, regardless of exposure scenario (acute dietary, short- or intermediate-term, chronic, or cancer). Table 1 provides a summary. Specifics regarding the comparison of model estimates to DWLOC values are given in steps 8 and 9.

Table 1. DWLOCs Compared to Model Estimates of Pesticide Concentrations in Ground and Surface Water.

DWLOC Values	GENEEC	FIRST	PRZM/EXAMS	SCI-GROW
$DWLOC_{ACUTE}$	maximum concentration	maximum concentration	maximum concentration	90-day average concentration
$DWLOC_{CHRONIC}$	**56-day average ÷ 3**	**annual average**	**annual average and 36-year mean**	90-day average concentration
$DWLOC_{CANCER}$	**56-day average ÷ 3**	**annual average**	annual average and 36-year mean	90-day average concentration
$DWLOC_{SHORT-TERM}$	**56-day average ÷ 3**	**annual average**	annual average and 36-year mean	90-day average concentration
$DWLOC_{INTERMEDIATE-TERM}$	**56-day average ÷ 3**	**annual average**	annual average and 36-year mean	90-day average concentration

Step 8: Characterizing the Results of the Screening-Level Assessment Using GENEEC or FIRST and SCI-GROW

- **If the models' estimates of a pesticide's concentration in ground and surface water (inclusive of relevant degradation products) are less than HED's levels of comparison for drinking water (DWLOCs), HED concludes with reasonable certainty that the exposure to the pesticide in drinking water is likely to be insignificant, and the associated human health risks are not of concern. Qualitative risk language should be used to characterize the risk, and/or**

a table of DWLOC values for comparison to the model estimates can be provided. An example table comparing acute DWLOC values to the appropriate model concentration estimates is provided below. Similar tables can be prepared for the chronic, cancer, short- and intermediate portions of the aggregate risk assessment.

Population Subgroup	aPAD (mg/kg)	1-Day Food Exposure (mg/kg/day)	Allowable One-Day Water Exposure (mg/kg/day)	% aPAD	GW Conc.* (ppb)	SW Conc.* (ppb)	Acute DWLOC (μg/L)
US population							
Female Subgroup							
Children's Subgroup							
Infant's Subgroup							

*** Groundwater (GW) concentration from SCI-GROW represents a 90-day average. Surface water (SW) concentration from GENEEC or FIRST represents an estimated maximum concentration.**

! **The following standard language provides an example of qualitative risk language that could be used for a pesticide with food uses, but no residential uses, for which acute, chronic and cancer risk assessments are required, and where the estimated concentrations in surface and ground water are less than HED's levels of comparison for drinking water for <u>all</u> risk assessments required.**

> **"***OPP has calculated drinking water levels of comparison (DWLOCs) for acute exposure to [chemical] in surface and ground water for [population subgroups]. They are [X, Y, ...] ppb, respectively. For chronic (non-cancer) exposure to [chemical] in surface and ground water, the drinking water levels of comparison are [X, Y,...] ppb for [population subgroup], respectively. For chronic (cancer) exposure to [chemical] in surface and ground water, the drinking water levels of comparison are [X, Y,...] ppb, respectively for [population subgroups]. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM analysis) was subtracted from the acute RfD or PAD to obtain the allowable acute (1-day) exposure to [chemical] in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM) was subtracted from the chronic RfD or PAD to obtain the allowable chronic (non-cancer) exposure to [chemical] in drinking water. To calculate the DWLOC for chronic exposures relative to a carcinogenic toxicity endpoint, the chronic (cancer) dietary food exposure (from the DEEM analysis) was subtracted from the ratio of the negligible cancer risk to the q* to obtain the allowable chronic (cancer) exposure to [chemical] in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption rates.*

Estimated maximum concentrations of [chemical] in surface and ground water are [X] and [Y] ppb, respectively. Estimated average concentrations of [chemical] in surface and ground water are [X] and [Y] ppb, respectively. [Note: For the purposes of the screening-level assessment, the maximum and average concentrations in ground water are not believed to vary significantly.] The maximum estimated concentrations of [chemical] in surface and ground water are less than OPP's levels of comparison for [chemical] in drinking water (DWLOC acute) as a contribution to acute aggregate exposure. The estimated average concentrations of [chemical] in surface and ground water are less than OPP's levels of comparison for [chemical] in drinking water (DWLOC chronic and cancer) as a contribution to chronic aggregate exposure for cancer and non-cancer effects. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of [chemical] in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in aggregate risk estimates that exceed HED's levels of concern at this time.

OPP bases this determination on a comparison of estimated concentrations of [chemical] in surface waters and ground waters to back-calculated "levels of comparison" for [chemical] in drinking water. These concentration estimates from screening-level models are considered to be upper bound for the purposes of comparison to drinking water levels of comparison. These levels of comparison in drinking water were determined after OPP had considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of [chemical] in surface and ground waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of [chemical] on drinking water as a part of the aggregate risk assessment process.

! **If the models' estimates of pesticide concentrations in surface and ground water are greater than HED's levels of comparison for drinking water (DWLOCs), HED notifies EFED that a refined screening-level assessment is needed. HED may initiate a meeting with EFED and invites RD/SRRD to discuss the necessary refinement.**

Step 9: Characterizing the Results of the Screening-Level Assessment Using PRZM/EXAMS and SCI-GROW

For surface water, when the maximum concentration estimate from the GENEEC or FIRST models are greater than the $DWLOC_{acute}$, and/or the longer-term concentration estimates from the tier 1 models are greater than the $DWLOC_{cancer}$ or $DWLOC_{chronic}$ values, HED requests refined

estimates from the PRZM/EXAMS surface water model from EFED. HED requests a maximum (peak), the annual average, and 36-year mean concentration estimates from EFED for the pesticide (inclusive of relevant degradation products) in surface water. HED compares the refined model estimates to the appropriate DWLOC values. An annual average concentration may be appropriate for comparison against DWLOC chronic values and a multi-year mean may be more appropriate for comparison to cancer DWLOC values when a q* is used to quantify cancer risks. HED requests both values from EFED. If the tier 2 model estimates from PRZM/EXAMS are less than the DWLOCs, HED will use a similar approach as above in Step 8 for a qualitative risk assessment.

- **For surface water, if the screening-level model estimates from PRZM/EXAMS are still greater than HED's levels of comparison for drinking water (DWLOCs), HED again notifies EFED, and EFED may conduct a detailed review and analysis of all available monitoring data, and determines if they are reliable and appropriate to use for an assessment of the pesticide's impacts on drinking water or EFED refines the screening-level drinking water concentration estimates as much as possible.**

- **For ground water, a tier 2 model is not yet available. EFED will review all monitoring data to determine if they are appropriate for a human health exposure and risk assessment.**

Step 10: EFED and HED Work Cooperatively to Prepare a Screening-Level Exposure Assessment using Monitoring Data.

- **Once EFED determines the appropriateness and reliability of available ground and surface water monitoring data, EFED provides maximum, annual average, and multi-year mean concentrations from monitoring data for all regions/states/counties for which monitoring data are available, appropriate, and reliable to HED.**

- **EFED provides the concentrations requested and characterizes the monitoring data in a memo to HED. The characterization includes as much of the following information as possible:**

    - **Source of Data (STORET, Pesticides in Groundwater Database, USGS, other)**
    - **Location of monitoring (the region/state/county where samples were taken, and an indication as to whether the monitoring data is for ground or surface water, and whether or not it represents drinking water sources (raw water at intakes versus treated drinking water) or ambient water quality)**
    - **Sampling Dates**
    - **Total Number of Samples Analyzed**
    - **Total Number of Samples with Detects**
    - **The maximum concentration, average annual, and multi-year mean concentrations, and the range of concentrations.**
    - **Limits of Detection (LOD) and Limits of Quantification (LOQ)**
    - **Spatial overlap of monitoring data with potential use areas**
    - **Depth of well water sampled for ground-water monitoring**
    - **Water sources (lake, river, stream, etc.) for surface-water monitoring**

- -- **A clear statement regarding the level of confidence in monitoring data (the confidence level associated with the monitoring data, i.e., high, medium or low),**
- -- **A statement regarding what the monitoring data represent (e.g., an upper bound, lower bound, or something in between).**
- -- **Estimates of populations living in the areas sampled.**

! **HED may elect simply to compare the concentration estimates derived from available monitoring data to the appropriate DWLOC values, and present the information in a table comparing DWLOC values to concentration estimates from the monitoring data. From the monitoring data, estimates of maximum concentrations are compared to $DWLOC_{ACUTE}$ values, and estimates of long-term average concentrations (annual averages or multi-year means) are compared to all other DWLOC values (as described in Step 7 for model estimates).**

! **Alternatively, HED may calculate the drinking water exposure using values from monitoring data in the following equations for adult males, adult females, infants/children, respectively :**

$$Exposure\ (mg/kg/day) = \frac{concentration\ water\ (\mu g/L)\ x\ 10^{-3}\ (mg/\mu g)\ x\ 2\ L/day}{70\ kg\ for\ adults\ (male)}$$

$$Exposure\ (mg/kg/day) = \frac{concentration\ water\ (\mu g/L)\ x\ 10^{-3}\ (mg/\mu g)\ x\ 2\ L/day}{60\ kg\ for\ adults\ (female)}$$

$$Exposure\ (mg/kg/day) = \frac{concentration\ water\ (\mu g/L)\ x\ 10^{-3}\ (mg/\mu g)\ x\ 1\ L/day}{10\ kg\ for\ children}$$

! **In the above equations, for acute exposure calculations, HED uses maximum concentration values for surface and ground water from EFED. For chronic (non-cancer) exposure calculations, HED may use average annual concentration values for surface and ground water from EFED. For cancer (q* approach) exposure calculations, HED may use multi-year mean concentration values for surface and ground water if available.**

! **The risk metrics (% RfD or PAD, and MOE) provided in HED's "Guidance for Performing Aggregate Exposure and Risk Assessments" can be used to estimate the risk inclusive of the screening-level estimate of drinking water exposure based on monitoring**

data.

- **HED characterizes the drinking water exposure in light of EFED's characterization of the data and confirms their understanding of the characterization with EFED. HED indicates if the monitoring data represent drinking water (treated or raw) or ambient water quality, and if pesticide use is associated with the areas monitored. HED states the level of confidence in the data. HED states if the screening-level risk estimate is associated with a specific region or regions of the country or a specific state or states. If population estimates are provided for specific regional monitoring data, HED discusses exposure in terms of population potentially exposed.**

- **If the concentration estimates from the monitoring data are less than the DWLOC values,**

OR

the aggregate risk estimates inclusive of drinking water exposure are below HED's level of concern (i.e., less than 100% of the RfD or PAD), HED finalizes its risk characterization, and concludes with reasonable certainty that residues of the pesticide in drinking water are not expected to result in aggregate risk estimates that exceed HED's levels of concern.

- **If the concentration estimates from the monitoring data are greater than the DWLOC values or the aggregate risk estimates are above HED's levels of concern (i.e., greater than 100% of the RfD or PAD), and HED has refined its exposure assessment as to residues in food as much as possible, HED may in consultation with EFED elect to further refine the drinking water exposure assessment by using distributions of monitoring data in the DEEM program and where applicable probabilistic techniques of exposure analysis. This step adds another refinement to the screening-level process allowing incorporation of specific information on body weights and drinking water consumption available through the DEEM program into the drinking water exposure assessment. The need for more refined screening-level assessments and/or quantitative estimates of drinking water exposure for a compound will be determined on a case-by-case basis. The procedures, models, and monitoring data needed to develop more refined screening-level assessments and/or quantitative estimates of drinking water exposures to pesticides are beyond the scope of this document; they will be discussed in future documents.**

- **If the models' concentration estimates are greater than the DWLOC values, and adequate monitoring data are <u>not</u> available, interim risk management and monitoring data or other sources of information on the pesticide's impact on water may be required as a part of reregistration for RED chemicals, as a condition of registration for new chemicals, or as a condition of extending a tolerance or adding a new use. In general, chemicals needing interim risk mitigation will be handled on a case-by-case basis.**

Policy Not Rules

The policy document discussed in this notice is intended to provide guidance to EPA personnel and decision-makers, and to the public. As a guidance document and not a rule, the

policy in this guidance is not binding on either EPA or any outside parties. Although this guidance provides a starting point for EPA risk assessments, EPA will depart from its policy where the facts or circumstances warrant. In such cases, EPA will explain why a different course was taken. Similarly, outside parties remain free to assert that a policy is not appropriate for a specific pesticide or that the circumstances surrounding a specific risk assessment demonstrate that a policy should be abandoned.

APPENDIX I

EXAMPLE CALCULATIONS FOR SHORT- AND INTERMEDIATE-TERM DWLOCS AND DRINKING WATER EXPOSURE

Case 1: Calculating $DWLOC_{SHORT-TERM}$ using the Reciprocal MOE Equation

An example summary of the endpoints selected by the HIARC are included as Table 1.

Table 1. Toxicology Endpoints for Lamda-cyhalothrin*

Exposure Route	Dose (mg/kg/day)	Endpoint Selected/study
Acute Dietary	NOAEL=0.5 mg/kg/day RfD= 0.005 mg/kg/day, UF= 100** MOE = 100	Gait abnormalities in dogs in a chronic toxicity study.
Chronic Dietary	NOAEL=0.1 mg/kg/day RfD= 0.001 mg/kg/day, UF= 100 MOE = 100	Neurotoxicity, ataxia and convulsions in dogs in a chronic toxicity study .
Short-term Dermal	NOAEL=10.0 mg/kg/day, UF = 100 MOE = 100	Mortality, clinical signs and effects on body weight and food consumption in a 21-day dermal rat study.
Intermediate-term Dermal	NOAEL=10.0 mg/kg/day, UF = 100 MOE = 100	Mortality, clinical signs and effects on body weight and food consumption in a 21-dermal study in rats
Chronic-term Dermal	NOAEL=0.1 mg/kg/day, UF = 100 MOE = 100	Neurotoxic clinical signs in both sexes of dogs in a chronic toxicity study.
Inhalation (any time period)	NOAEL=0.3 µg/L, UF = 100 (0.08 mg/kg/day) MOE = 100	Neurotoxic clinical signs, alterations in clinical pathology and alveolitis in rats in a 21-day inhalation study

*** Taken from memo S. Weiss, 11/16/98, D249214, T:\HED\REVIEWS\128897\SEC18. Aggregate assessment is appropriate because of similarity in systemic toxicity observed in rats via all routes. ** Uncertainty Factor (UF) is equivalent to the acceptable Margin of Exposure (MOE).**

To use the following equations, the following conditions must apply: all acceptable MOEs must be identical for all MOEs to be included in the short-term risk assessment. Based on the toxicity endpoint information above, all acceptable MOEs are 100, and no oral endpoint for hand-to-mouth residential exposure was identified. In this case, use the acute dietary endpoint (NOAEL) to incorporate dietary (food and water), and residential hand-to-mouth exposures in the aggregate risk assessment. A short-term residential exposure scenario was identified and includes a dermal and inhalation exposure route, but no oral exposure route. To complete the aggregate short-term exposure and risk assessment, chronic dietary (food and drinking water) and residential (1 to 7 day) dermal and inhalation exposures must be included.

For infants, the pertinent short-term exposure routes are:

the short-term residential high-end dermal exposure of 1.28 E-3 mg/kg/day,
the short-term residential high-end inhalation exposure of 1.68 E-5 mg/kg/day, and
the average (chronic) exposure from food of 7.3 E-5 mg/kg/day.

Solve the reciprocal MOE equation below for MOE_{water} to determine the $DWLOC_{short\text{-}term}$ for infants.

$$\text{Aggregate MOE} = \frac{1}{\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{WATER}} + \frac{1}{MOE_{ORAL}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}}}$$

$$MOE_{WATER} = \frac{1}{\frac{1}{MOE_{AGG}} - \left[\frac{1}{MOE_{FOOD}} + \frac{1}{MOE_{DERMAL}} + \frac{1}{MOE_{INHALATION}} + \frac{1}{MOE_{ORAL}}\right]}$$

Where Aggregate MOE = 100 (based on all acceptable MOEs being equal to 100),
MOE_{FOOD} = 0.5 mg/kg/day ÷ 7.3 E-5 mg/kg/day = 6850,
MOE_{DERMAL} = 10 mg/kg/day ÷ 1.28 E-3 mg/kg/day = 7800,
$MOE_{INHALATION}$ = 0.08 mg/kg/day ÷ 1.68 E-5 mg/kg/day = 4760,
MOE_{ORAL} = Not applicable to this risk assessment and the term is removed from equation.

Substituting these calculated MOEs into the equations above and solving for MOE_{WATER} gives:

$$100 = \frac{1}{\frac{1}{6850} + \frac{1}{MOE_{WATER}} + \frac{1}{7800} + \frac{1}{4760}}$$

$$MOE_{WATER} = \frac{1}{\frac{1}{100} - \left[\frac{1}{6850} + \frac{1}{7800} + \frac{1}{4760}\right]}$$

MOE_{WATER} = 1 ÷ 9.5 E-3 = 105

$$105 = \frac{\text{Short-term oral or acute dietary NOAEL}}{\text{Allowable Short-Term Water Exposure}}$$

$$4.76\text{ E-3 mg/kg/day} = \frac{0.5\text{ mg/kg/day}}{105}$$

Substituting the Water Exposure value, the Short-term DWLOC for infants was calculated as follows:

$$\text{DWLOC}(\mu\text{g/L}) = \frac{\text{4.76 E-3 (mg/kg/day) x 10 (kg)}}{\text{(1E-3 mg/}\mu\text{g) x 1 (L/day)}} = 48 \text{ ug/L (ppb)}$$

Compare the $DWLOC_{SHORT\text{-}TERM}$ to the appropriate model estimates given below.

DWLOC Values (ppb)	GENEEC	FIRST (ppb)	PRZM/EXAMS (ppb)	SCI-GROW (ppb)
$DWLOC_{SHORT\text{-}TERM}$ (48 ppb)	56-day average ÷ 3	annual average	annual average and 36-year mean	90-day average concentration

[Note: $DWLOC_{INTERMEDIATE\text{-}TERM}$ is calculated similarly, but the intermediate-term oral or chronic dietary NOAEL is used, and the appropriate intermediate-term dermal exposure, endpoint and UFs are used.]

Case 2: Calculating $DWLOC_{SHORT\text{-}TERM}$ using an Alternative Approach

For the case where the allowable exposure (the RfD or PAD) for all pertinent routes of exposure (dietary (food and water) oral exposures, non-dietary residential dermal, inhalation or oral hand-to-mouth type exposures) included in the short-term or intermediate-term risk assessment are the same (i.e., the NOAELs and UFs selected for each pertinent route of exposure are identical), the simplified equation given below can be used. For example, this situation occurs when the endpoints selected for any short-term residential dermal, inhalation, and non-dietary, inadvertent oral (hand-to-mouth) exposures are the same as those selected for the acute dietary oral (food and water) exposures. This is also the case for the $DWLOC_{INTERMEDIATE\text{-}TERM}$ when the endpoints selected for any intermediate-term dermal, inhalation, and non-dietary, inadvertent oral (hand-to-mouth) exposures are the same as those selected for the chronic dietary oral (food and water) exposures.

Such a case is given in Table 2 showing hypothetical results from a HIARC meeting. Note that in this case, the acute dietary NOAEL, the short-term dermal and inhalation NOAELs (endpoints) and UFs are all identical.

$$DWLOC_{ST}\ (ug/L) = \frac{[ST\ water\ exposure\ (mg/kg\ bw/day)\ x\ body\ weight\ (kg)]}{[consumption\ (L/day)\ x\ 10^{-3}\ mg/ug]}$$

$$ST\ water\ exposure\ (mg/kg/day) = [AcutePAD - (\ avg.\ food + high\text{-}end\ residential\ exposure)\ (mg/kg/day)\ ]$$

Table 2. Toxicology Endpoints for Chemical X*

Exposure Route	Dose (mg/kg/day)	Endpoint Selected/study
Acute Dietary	NOAEL=10.0 mg/kg/day RfD= 0.01 mg/kg/day, UF= 100 MOE = 100	General neurotoxic effects (gait abnormalities).
Chronic Dietary	NOAEL=0.1 mg/kg/day RfD= 0.001 mg/kg/day, UF= 100 MOE = 100	Neurotoxicity, ataxia and convulsions in dogs in a chronic toxicity study .
Short-term Dermal	NOAEL=10.0 mg/kg/day, UF = 100 MOE = 100	General neurotoxic effects (convulsions).
Intermediate-term Dermal	NOAEL=10.0 mg/kg/day, UF = 100 MOE = 100	Mortality, clinical signs and effects on body weight and food consumption in a 21-dermal study in rats
Inhalation (any time period)	NOAEL= 10 mg/kg/day, UF = 100 MOE = 100	General neurotoxic effects (clinical signs, weight gain/loss).

*** Hypothetical values for purposes of example used.**

Based on the toxicity endpoint information above, all acceptable MOEs are 100, and no oral endpoint for hand-to-mouth residential exposure was identified. In this case, use the acute dietary endpoint (NOAEL) to incorporate dietary (food and water), and residential hand-to-mouth exposures in the aggregate risk assessment. A short-term residential exposure scenario was identified and includes a dermal and inhalation exposure route, but no oral exposure route. To complete the aggregate short-term exposure and risk assessment, chronic dietary (food and drinking water) and short-term (1 to 7 day) residential exposures must be included.

For infants, the pertinent short-term exposure routes are:

the short-term residential high-end dermal exposure of 1.28 E-3 mg/kg/day,
the short-term residential high-end inhalation exposure and 1.68 E-5 mg/kg/day, and
the average (chronic) exposure from food of 7.3 E-5 mg/kg/day.

The short-term aggregate risk including drinking water exposure can be calculated using the

equations and approach in Case 1 by solving the reciprocal MOE equation below for MOE_{water} to determine the $DWLOC_{short\text{-}term}$ for infants. It can also be solved using the simpler equation below for calculating $DWLOC_{short\text{-}term}$ values. The alternative approach is only valid for cases where all endpoints and UFs included in the calculation for incorporating food, water, and residential exposures are identical. If in doubt regarding the use of the approach in Case 2, use the reciprocal MOE method to check the result. Either approach should lead to the same result.

Solving for the short-term (ST) water exposure and the $DWLOC_{ST}$ for infants, gives:

Where, the Acute RfD = 0.01 mg/kg/day, given the information above on exposure, then

Short-term water exposure = 0.01 mg/kg/day - [(7.3 E-5 + 1.28 E-3 + 1.68 E-5) mg/kg/day]

Short-term water exposure = 0.01 mg/kg/day - 0.0013 mg/kg/day = 0.0086 mg/kg/day

$DWLOC_{ST}$ = [0.0086 mg/kg/day x 10 kg bwt] ÷ [1 L/day x 1 E-3 mg/ug] = 86 ug/L (ppb)

Compare the $DWLOC_{SHORT\text{-}TERM}$ to the appropriate model estimates given below.

DWLOC Values (ppb)	GENEEC	FIRST (ppb)	PRZM/EXAMS (ppb)	SCI-GROW (ppb)
$DWLOC_{SHORT\text{-}TERM}$ (86 ppb)	56-day average ÷ 3	annual average	annual average and 36-year mean	90-day average concentration

[Note: in this example, to calculate the intermediate-term DWLOC, the reciprocal MOE method is needed because the chronic dietary NOAEL (0.1 mg/kg/day) is not equal to the intermediate dermal and inhalation endpoints (10 mg/kg/day, each).]

Case 3: Calculating $DWLOC_{SHORT\text{-}TERM}$ using the ARI Method

Based on the toxicity endpoint information below in Table 3, not all of the acceptable MOEs are identical. The short-term dermal endpoint has a UF/MOE of 1000 because of the FQPA 10X safety factor applied for infants and children, while the assessments for incorporating food, water, and inhalation exposures have UFs/MOEs of 100. In this case, use the ARI method to calculate $DWLOC_{SHORT\text{-}TERM}$ values for the short-term risk assessments. No oral endpoint for hand-to-mouth residential exposure was identified, therefore, use the acute dietary endpoint (NOAEL) to incorporate dietary (food and water), and residential hand-to-mouth exposures in the aggregate risk assessment. A short-term residential exposure scenario was identified and includes a dermal and inhalation exposure route, but no oral exposure route. To complete the aggregate short-term exposure and risk assessment, chronic dietary (food and drinking water) and short-term (1 to 7 day) residential dermal and inhalation exposures must be included.

Table 3. Toxicology Endpoints for Chemical X*

Exposure Route	Dose (mg/kg/day)	Endpoint Selected/study
Acute Dietary	NOAEL=0.5 mg/kg/day RfD= 0.005 mg/kg/day, UF= 100 MOE = 100	Gait abnormalities in dogs in a chronic toxicity study.

Table 3. Toxicology Endpoints for Chemical X*		
Exposure Route	**Dose (mg/kg/day)**	**Endpoint Selected/study**
Chronic Dietary	**NOAEL=0.1 mg/kg/day RfD= 0.001 mg/kg/day, UF= 100 MOE = 100**	**Neurotoxicity, ataxia and convulsions in dogs in a chronic toxicity study .**
Short-term Dermal	**NOAEL=10.0 mg/kg/day, UF = 100, FQPA Factor = 10 MOE = 1000**	**Mortality, clinical signs and effects on body weight and food consumption in a 21-day dermal rat study.**
Intermediate-term Dermal	**NOAEL=10.0 mg/kg/day, UF = 100 MOE = 100**	**Mortality, clinical signs and effects on body weight and food consumption in a 21-dermal study in rats**
Chronic-term Dermal	**NOAEL=0.1** mg/kg/day**, UF = 100 MOE = 100**	**Neurotoxic clinical signs in both sexes of dogs in a chronic toxicity study.**
Inhalation (any time period)	**NOAEL= 0.3 mg/kg/day, UF = 100 (0.08 mg/kg/day) MOE = 100**	**Neurotoxic clinical signs, alterations in clinical pathology and alveolitis in rats in a 21-day inhalation study**

*** Hypothetical values for purposes of example used.**

For infants, the pertinent short-term exposure routes are:

the short-term residential high-end dermal exposures of 1.28 E-3 mg/kg/day,
the short-term residential high-end inhalation exposures of 1.68 E-5 mg/kg/day, and
the average exposure from food of 7.3 E-5 mg/kg/day.

The short-term aggregate risk including drinking water exposure can be calculated using the ARI method for aggregating exposure. The equations below can be solved for MOE_{WATER} to determine the $DWLOC_{SHORT\text{-}TERM}$ for infants.

$$\text{Aggregate ARI} = \frac{1}{\frac{1}{ARI_{FOOD}} + \frac{1}{ARI_{WATER}} + \frac{1}{ARI_{ORAL}} + \frac{1}{ARI_{DERMAL}} + \frac{1}{ARI_{INHALATION}}}$$

$$ARI_{WATER} = \frac{1}{\frac{1}{ARI_{AGG}} - \left[\frac{1}{ARI_{FOOD}} + \frac{1}{ARI_{DERMAL}} + \frac{1}{ARI_{INHALATION}} + \frac{1}{ARI_{ORAL}}\right]}$$

Where, ARI = $[MOE_{CALCULATED} \div MOE_{ACCEPTABLE}]$,
ARI_{AGG} = 1,
$ARI_{FOOD} = [MOE_{FOOD} \div$ MOE (acceptable)] = [(0.5 ÷ 7.3 E-5) (mg/kg/day)] ÷ 100 = 69,
$ARI_{DERMAL} = [MOE_{DERMAL} \div$ MOE (acceptable)] = [(10 ÷ 1.28 E-3)(mg/kg/day)] ÷ 1000 = 8 ,
$ARI_{INHALATION} = [MOE_{INHALATION} \div$ MOE (acceptable)] = [(0.08 ÷ 1.68 E-5) (mg/kg/day)] ÷ 100 = 48, and
ARI_{ORAL} = not applicable to this risk assessment and the term is removed from the equation.

Substituting the calculated and acceptable MOEs into the equations above and solving for ARI_{WATER} gives:

$$ARI_{WATER} = \frac{1}{\frac{1}{1} - \left[\frac{1}{69} + \frac{1}{8} + \frac{1}{48}\right]}$$

ARI_{WATER} = 1.19 = [MOE_{WATER} ÷ $MOE_{ACCEPTABLE}$]; Where the acceptable MOE for water is 100.

MOE_{WATER} = 1.19 x 100 = 119

$$119 = \frac{\text{Short-term oral or acute dietary NOAEL}}{\text{Short-term Water Exposure}}$$

$$\text{Short-term Water Exposure (mg/kg/day)} = \frac{0.5 \text{ mg/kg/day}}{119} = 4.2 \text{ E-3 mg/kg/day}$$

Substituting the ST Water Exposure value, the Short-term DWLOC for infants:

$$DWLOC(\mu g/L) = \frac{4.2 \text{ E-3 (mg/kg/day) x 10 (kg)}}{(1\text{E-3 mg}/\mu g) \text{ x 1 (L/day)}} = 42 \text{ ug/L}$$

Compare the $DWLOC_{SHORT-TERM}$ to the appropriate model estimates given below.

DWLOC Values (ppb)	GENEEC	FIRST (ppb)	PRZM/EXAMS (ppb)	SCI-GROW (ppb)
$DWLOC_{SHORT-TERM}$ (42 ppb)	56-day average ÷ 3	annual average	annual average and 36-year mean	90-day average concentration

[Note: $DWLOC_{INTERMEDIATE-TERM}$ is calculated similarly, but the intermediate-term oral or chronic dietary NOAEL is used, and the appropriate intermediate-term dermal exposure, endpoint and UFs are used.]

***Other examples of calculations can be found in the Bensulide and Iprodione REDs, and the Section 18 for Lamda-Cyhalothrin on Flax in North Dakota (T:\hed\reviews\122897\sec18).**

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