Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria

Recommendations from the Toxics Steering Group, Children's Environmental Health Subcommittee

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Table of Contents

List of Abbreviations

AT	Averaging time
ATSDR	The Agency for Toxic Substances and Disease Registry
BMC	Benchmark concentration
BMD	Benchmark dose
BMDL	Lower-bound confidence limit on the benchmark dose
CEHS	Children's Environmental Health Subcommittee of the Michigan TSG
CSA	Criteria Stakeholder Advisory Group (MDEQ)
CSEFH	Child-Specific Exposure Factors Handbook (EPA, 2008)
DDEF	Data-derived extrapolation factor
DR	Developmental and/or early-life reproductive adverse endpoint
DR RfV	Reference Value based on at least one critical DR toxicity endpoint
ED	Exposure duration
EF	Exposure frequency
EFH	Exposure Factors Handbook (EPA, 2011)
EHC	Environmental Health Criteria (WHO)
EPA	United States Environmental Protection Agency
FDA	United States Food and Drug Administration
IRIS	Integrated Risk Information System (EPA)
IURF	Inhalation unit risk factor
LOAEL	Lowest Observed Adverse Effect Level
MDEQ	Michigan Department of Environmental Quality
MDHHS	Michigan Department of Health and Human Services
MDARD	Michigan Department of Agriculture and Rural Development
MRL	Minimal Risk Level (ATSDR)
NAS/NRC	National Academy of Science, National Research Council
NOAEL	No Observed Adverse Effect Level
nonDR	Noncancer adverse endpoint other than DR
OECD	Organization for Economic Cooperation and Development
PBPK	Physiologically-based pharmacokinetic model
PCBs	Polychlorinated biphenyls
PDA	Pregnancy Discrimination Act of 1978
POD	Point of departure
RfC	Reference Concentration
RfD	Reference Dose
RfV	Reference Value for noncancer adverse effects (e.g., RfC, RfD, MRL)
RRD	Remediation and Redevelopment Division (MDEQ)
RSL	Regional Screening Level
SRC	Syracuse Research Corporation
TAG2	Technical Advisory Group for Exposure Assumptions
TCE	Trichloroethylene
TSD	Technical Support Document (Appendix A)

TSG	Toxics Steering Group (MDEQ, MDHHS, MDARD)
UF	Uncertainty factor
WHO	World Health Organization

Executive Summary

Background

The Michigan Department of Environmental Quality (MDEQ) Remediation and Redevelopment Division (RRD) develops generic cleanup criteria (generic criteria) under Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended, for approximately 300 hazardous substances. The generic criteria have not undergone a comprehensive update since they were originally promulgated in 2002. In anticipation of the next comprehensive update, the MDEQ convened an external Criteria Stakeholder Advisory group (CSA) in 2014 to make recommendations regarding the generic criteria update process. The CSA final report (CSA, 2014) recognized the need to protect public health and for generic criteria to be protective of sensitive toxic effects as stated in one of its guiding principles:

> *"The generic cleanup criteria need to be protective of public health and natural resources such that there are no unacceptable exposures to hazardous substances. Generic criteria are to be protective of the most sensitive toxic effect in a given exposure pathway for the hazardous substance in question."*

To protect for developmental and/or reproductive (DR) toxicity when it is the most sensitive toxic effect, the CSA made the following recommendations:

> ***2.1:*** *Receptor: Use an age-adjusted child plus adult receptor that, at present, assumes exposure across two age bins, except in the case of developmental toxicants.*
>
> ***2.2:*** *Guidance: Use EPA information to develop a process to account for those chemicals, or classes of chemicals, that have documented developmental or reproductive effects.*
>
> ***2.3:*** *Descriptive Language: Use current Part 201 rules (R299.49 (DD)) that allows the agency to regulate developmental and reproductive toxicants to protect sensitive subpopulations from these substances on a chemical-specific basis. For developmental and reproductive toxicants, the MDEQ should evaluate if the age-adjusted child plus adult receptor is protective of childhood and early-life-stage exposures on a chemical-specific basis*.

In line with these recommendations, RRD requested the assistance of the Toxics Steering Group (TSG) Children's Environmental Health Subcommittee (CEHS) to develop a process to generate criteria that address noncancer DR toxicity. This process will assist the MDEQ in establishing a consistent approach to addressing chemicals with DR toxicity and includes identifying available DR toxicity values and deriving DR toxicity values. This process will assure that cleanup criteria for various exposure pathways are adequately protective of the most sensitive endpoint based on the information available for a hazardous substance.

The CEHS evaluated the current MDEQ approach, as well as available guidance documents from the U.S. Environmental Protection Agency (EPA) and other national, international, and state agencies, to develop the following process. A review of the concepts and brief description of available guidance is included in Appendix A.

This process also considers the Part 201 statute and rules requirements. The specific regulatory language that requires consideration includes:

- **MCL 324.20120a(4)** *If a hazardous substance poses a risk of both cancer and 1 or more adverse health effects other than cancer, cleanup criteria shall be derived under this section for the most sensitive effect.*

- **MCL 324.20120b(2)** *Site-specific criteria approved under subsection (1) may, as appropriate:*
  (b) Alter any value, parameter, or assumption used to calculate generic criteria, with the exception of the risk targets specified in section 20120a(4).

- **R 299.34(3)** *The department may calculate generic cleanup criteria for certain hazardous substances using exposure assumptions other than those shown in the algorithms in these rules if either of the following conditions is satisfied:*
  (a) A hazardous substance causes an adverse effect in a sensitive subpopulation that is not adequately protected or represented by the generic exposure assumptions.
  (b) The toxicokinetics of a hazardous substance are not best represented by the average daily dose, when accounting for the most sensitive effect.

Identifying and Calculating Criteria for a Hazardous Substance with Noncancer DR Toxicity

Developmental toxicity means adverse outcomes induced during exposure at any early-life stage from preconception through adolescence (EPA, 2006; WHO, 2011). This toxicity can occur at any point in the life span and may include: (1) death; (2) structural abnormality; (3) altered growth; and/or (4) functional deficiency (EPA, 1991; EPA, 2006; WHO, 2011).

Reproductive toxicity manifests as harmful effects on sexual function and fertility. This can include changes to the female or male reproductive organs, the related endocrine system, and/or pregnancy outcomes. *For reproductive effects, the process described below is intended to address those that occur as a result of early-life exposures (i.e., from preconception through adolescence).*

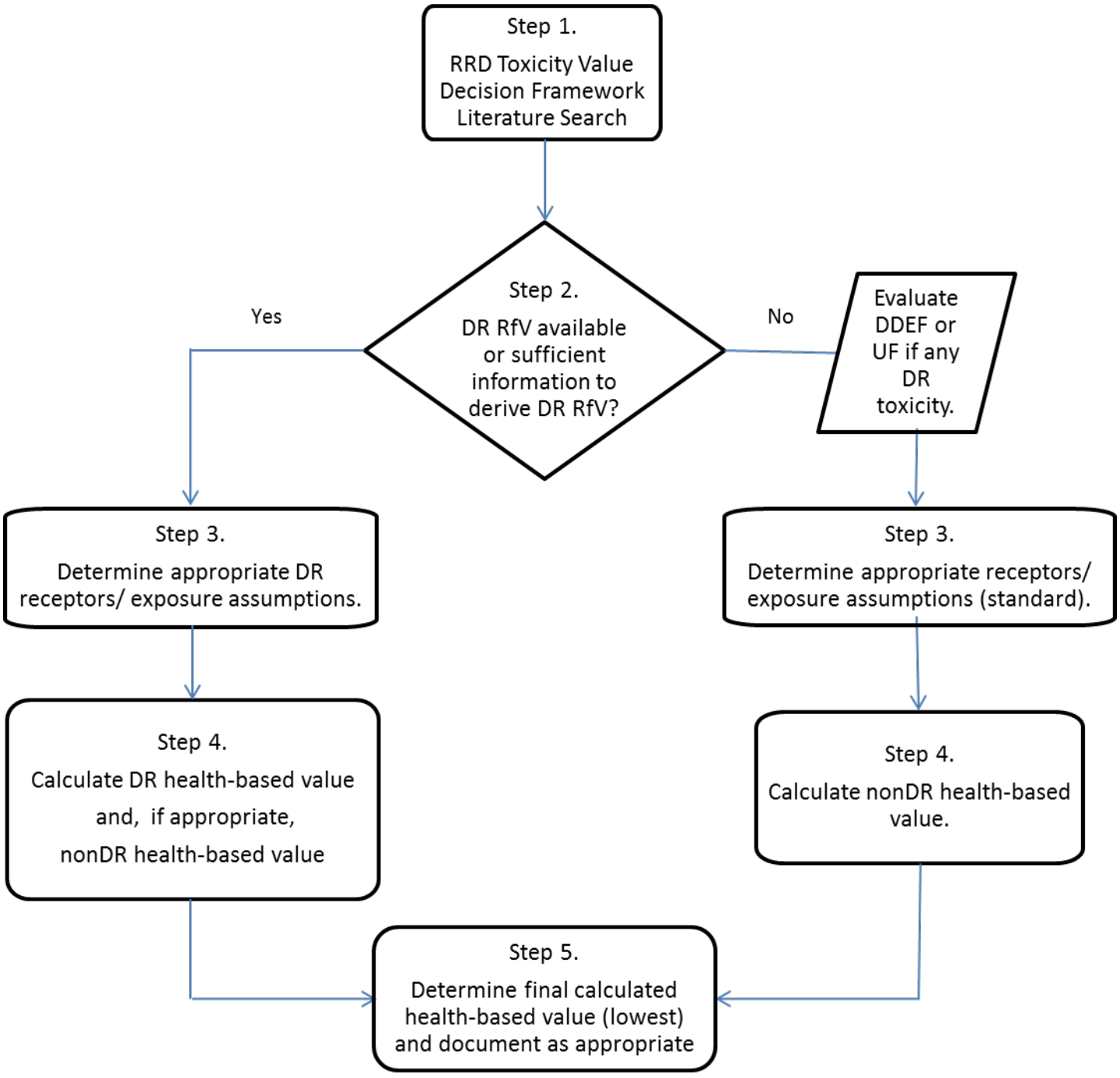
The process to evaluate a hazardous substance for DR toxicity is similar to evaluating other toxicity endpoints. A literature search is conducted to determine if there are existing toxicity values, or if other information or data are available to develop a toxicity value for various DR toxicological endpoints (e.g., organ or tissue damage, functional changes). DR toxicity values can include existing noncancer reference values (RfV) (e.g., Reference Dose [RfD], Reference

Concentration [RfC], Minimum Risk Level [MRL]). Evaluation of information from the literature search must determine if there are noncancer toxicity endpoints that occur after early-life exposure (DR toxicity).

The appropriate receptor and exposure assumptions are determined for each combination of hazardous substance, toxicity endpoint, exposure pathway, and land use. If there is a DR RfV or sufficient data to develop a DR RfV, then use that DR RfV to calculate health-based exposure pathway cleanup values with appropriate DR receptors. Compare the calculated DR health-based value to other cancer and/or nonDR noncancer health-based values to determine the final health-based cleanup values. The final cleanup value is the lowest value calculated using the appropriate algorithm for the critical cancer, mutagenic cancer, and noncancer (DR and/or NonDR) endpoints for the hazardous substance, exposure pathway, and land use. The final criterion is derived from either the final calculated health-based value or other value as required by statute or rule (e.g., state drinking water standard). Any limitations or considerations for the appropriate use of criteria for a hazardous substance are documented (e.g., footnotes) including those for DR toxicity.

Figure 1 presents the general steps in the process for establishing DR toxicity endpoints and development of DR health-based cleanup values. Detailed DR toxicity evaluation steps are outlined in the next section and a more detailed process flow chart that describes the substeps for each step follows in Figure 2.

Figure 1. General Process Description



RRD – Remediation and Redevelopment Division of the Michigan Department of Environmental Quality
DR RfV – Reference value for a developmental or developmental reproductive toxicity endpoint
DDEF – Data derived extrapolation factor
UF – Uncertainty Factor
DR – based on noncancer developmental and/or early-life reproductive toxicity
nonDR – based on noncancer toxicity that is not developmental or early-life reproductive

Detailed DR Toxicity Evaluation Process Steps

Step 1. RRD Toxicity Value Decision Framework Literature Search.

A literature search is conducted following the RRD Toxicity Value Decision Framework (Framework) (MDEQ, 2015) to identify the best available toxicity value(s) for a hazardous substance. **A literature search strategy specific to DR toxicity may need to be developed to ensure that relevant toxicity values and/or studies are located and evaluated.** [The current literature search strategy should be evaluated and refined, if appropriate, for DR toxicity in conjunction with the CEHS and RRD librarian.] The current literature search includes identification of information to determine the best available toxicity value(s) from all of the following Framework sources:

Tier 1. EPA Integrated Risk Information System (IRIS) (Note that for pesticides IRIS refers users to EPA Office of Pesticide Program documents for toxicity updates– these are an important best available toxicity value source, that includes DR toxicity values);
Tier 2. EPA Superfund Provisional Peer Reviewed Toxicity Value (PPRTV); or Agency for Toxic Substances and Disease Registry, Minimal Risk Levels for Hazardous Substances (ATSDR MRL);
Tier 3. Health Effects Assessment Summary Table (EPA); MDEQ existing value; Other state value; World Health Organization, Canadian or European Union value; *Potential future values from databases such as EPA's ToxCast, Read-across, Quantitative Structure Activity Relationships, or International Toxicity Estimates for Risk;* and
Tier 4. Search of published, with preference for peer reviewed, literature for a MDEQ toxicity assessment and RfV development.

Evaluation of the information from the literature search will result in one of the following outcomes:

Yes, information is found that allows evaluation of DR toxicity, proceed to Step 2a.
No, information is not found that allows for evaluation of DR toxicity, proceed to Step 2b.

Step 2. Determine Best Available RfV(s) and Document.

Once the available information regarding DR toxicity is evaluated, the DR and/or nonDR RfV(s) that are critical to protect for the most sensitive noncancer endpoint for a given exposure pathway are determined. **It is recommended that risk assessors refer to EPA risk assessment resources, including those listed in Appendix A, when identifying Tier 1-3 and setting Tier 4 values for DR toxicity. If a previously identified toxicity value is not based on a DR endpoint or critical effect, evidence is assessed to determine if the hazardous substance has DR effects.**

2a – An RfV protective of DR toxicity is available or can be determined with available information.

2a1 – The best available RfV (following the Framework) is based on DR toxicity (DR RfV). Determine appropriate DR receptor in Step 3 then proceed to step 4a1.

2a2 – The best available RfV (following the Framework) is a nonDR RfV. However, a DR RfV that meets the best available considerations is either available or can be determined.

- If Tier 1-3 DR RfV is available, determine appropriate DR receptors in Step 3 then proceed to step 4a2.
- If Tier 1-3 DR RfV is unavailable and information is sufficient to determine a DR RfV, derive the value and note it as Tier 4. Determine appropriate DR receptor in Step 3, then proceed to step 4a2. In this case, the MDEQ will provide an opportunity for stakeholders to give feedback on the data and methodology used to develop the toxicity value, per CSA Recommendation 1.3.

2a3 – Best available science indicates hazardous substance has DR toxicity, but an RfV specific for DR toxicity cannot be determined at this time. Evaluate if the best available nonDR RfV includes extrapolation (data-derived extrapolation factors [DDEF] or uncertainty factors [UF]) that adequately addresses DR toxicity.

- If so, use nonDR RfV and proceed to step 4b
- If not, apply an appropriate DDEF or UF to the nonDR RfV (EPA, 2014) and proceed to step 4b. Note that other preferred approaches may be available to adequately protect for DR toxicity for some hazardous substances (e.g., use of a surrogate chemical with similar structure or other toxicological characteristics).

2b - There is insufficient information to evaluate if hazardous substance has DR toxicity. Use best available nonDR RfV and proceed to step 4b.

Documentation related to DR toxicity is an important addition to the RRD chemical file. Information should be included in the chemical worksheet and file to document the DR information and the basis for the DR RfV.

Step 3. Determine DR Receptor Based on DR RfV.

As identified in Step 2, some hazardous substances will have sufficient information to determine a DR RfV. **Based on currently available information for both toxicity and exposure, the pregnant woman (to protect her fetus) and the young child are the key receptors for DR toxicants, unless there is chemical-specific information that a different critical window of exposure is appropriate.** The receptors appropriate for the DR RfV for each land use are determined to calculate exposure pathway health-based values. For most hazardous substances this will be a young child for residential land use and a pregnant woman for nonresidential land use.

The appropriate DR receptors for a DR RfV are as follows:

Residential land use:

1. A child (0-6 years);
2. A pregnant woman (single event for mortality, structural or functional abnormalities from fetal exposure; or full-term pregnancy (280 days) average for only altered growth from fetal exposure without mortality, structural or functional abnormalities or bioaccumulative chemicals); or
3. Other early-life exposure window based on chemical-specific information where there is a narrower or different critical window of exposure to be considered (e.g., adolescent receptor, prenatal only).

Nonresidential land use:

1. A pregnant woman (single event for mortality, structural or functional abnormalities from fetal exposure; full-term pregnancy (280 days) average for only altered growth from fetal exposure without mortality, structural or functional abnormalities or bioaccumulative chemicals); or
2. Other early-life exposure window based on chemical specific information that there is a narrower or different critical window of exposure to be considered (e.g., third trimester of pregnancy, preconception, working age adolescent).
    a) For bioaccumulative DR toxicants, the appropriate receptor is a woman of child-bearing age with a chronic exposure.[1]

Site-specific criteria:

The evaluation of site-specific criteria for approval will include assessment of DR toxicity. If DR toxicity is confirmed based on this process, the appropriate receptor for the toxicity endpoint, the land use at the site, and any accompanying exposure controls will be determined.

Step 4. Calculate Noncancer Cleanup Value(s).

This step uses the appropriate exposure pathway algorithm, toxicity value(s) from Step 2, and the receptor exposure assumptions from Step 3 to calculate the noncancer value(s). Exposure pathway algorithms for developmental receptors are provided in Appendix B. The noncancer health-based value(s) will be compared to the cancer value(s) (if available) to determine the final health-based cleanup value for the most sensitive effect, as indicated by the CSA recommendations.

[1] For bioaccumulative hazardous substances, the woman's body burden prior to pregnancy contributes more of an impact to the developing fetus than her exposure during pregnancy. See Appendix A for more information.

4a1 – Best available DR RfV only. Calculate noncancer exposure pathway health-based value using the best available DR RfV (Step 2a1) and the appropriate DR receptor (Step 3). Proceed to step 5a1.

4a2 – Best available NonDR RfV and DR RfV available. Calculate noncancer exposure pathway health-based values using both:

a) Best available nonDR RfV and the applicable receptor considering hazardous substance and land use (in most cases the default age-adjusted for residential land use and the default worker for nonresidential land use); and
b) Best available DR RfV (Step 2a2) and the appropriate DR receptor (Step 3).

The lower of the calculated values is the noncancer exposure pathways health-based value that protects for the most sensitive noncancer endpoint. Proceed to step 5a2.

4b - Calculate noncancer exposure pathway value using the best available nonDR RfV and the appropriate receptor considering hazardous substance and land use (e.g., in most cases typical generic receptors and exposure assumptions). Proceed to step 5b.

Step 5. Determine Final Health-based Value and Document DR Toxicity Information and Compliance Considerations.

The final health-based value is the lowest of the calculated cancer, DR noncancer, or nonDR noncancer cleanup values. Once the final criterion for the hazardous substance and exposure pathway has been determined, documentation related to DR toxicity is an important addition to the chemical file. **Identification of appropriate compliance considerations (e.g., averaging media concentrations over time) and priority setting with future updates of cleanup criteria should be included in the chemical file or worksheet.**

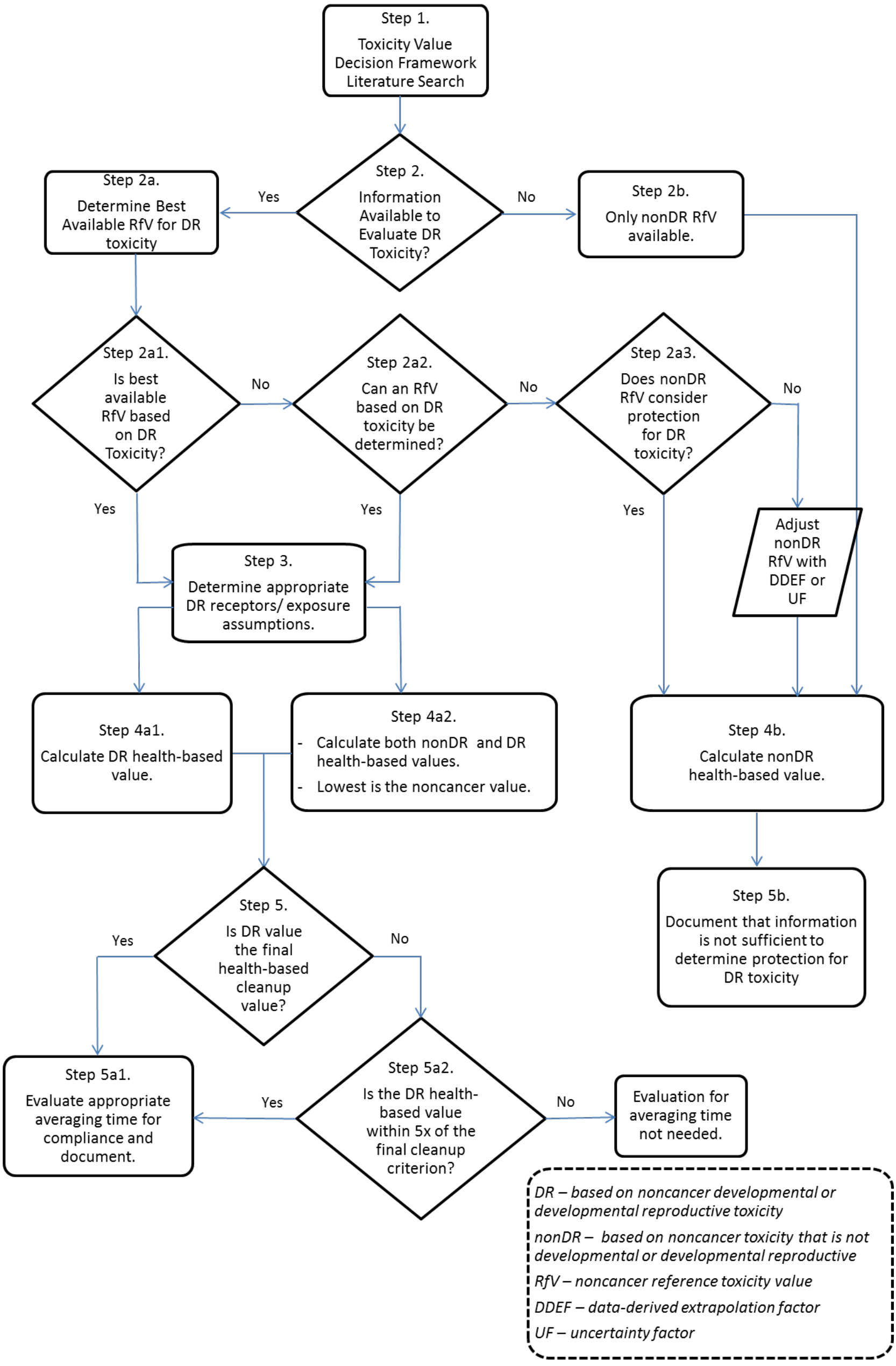
For some DR toxicity, single event prenatal exposures may result in adverse effects such as mortality and structural or functional abnormalities. As a result, it is not appropriate to average environmental media concentrations over time to compare to criteria. This applies to both residential and nonresidential land use. Although a child receptor typically has the lowest calculated value for generic residential land use, the criteria are also intended to protect for exposure to a pregnant woman in a residential setting. When chemical-specific information indicates that a different critical exposure window is appropriate, that critical exposure window should be the averaging time for environmental media concentrations.

5a1 – If a final criterion for the most sensitive effect (noncancer or cancer) is based on DR toxicity, documentation (e.g., criteria table footnote) will identify if evaluation of environmental media concentrations should be averaged over time. Hazardous substances that cause mortality, structural or functional abnormalities from fetal exposure are identified as single event DR toxicants. Hazardous substances that are bioaccumulative chemicals or are chemicals that cause altered growth from fetal exposure without mortality, structural or functional abnormalities are identified as full-term DR toxicants.

5a2 – If a final criterion for the most sensitive effect is based on an endpoint (noncancer or cancer) other than DR toxicity, but the calculated value using the DR RfV (if available) is based on mortality or structural or functional abnormalities and is less than five times higher than the final criterion, consider if it is appropriate to average environmental media concentrations over time as described above and document as appropriate. The five times value is based on consideration of exposure assumptions for average as compared to high end (to represent a single day or shorter term exposure) reported in Exposure Factors Handbook (EFH) (EPA, 2011).

5b – Document that the hazardous substance has insufficient information to determine if the criteria are adequately protective for DR toxicity. Identify the hazardous substance for a priority literature search for future criteria updates.

Figure 2. Process Flowchart to Address DR Toxicity in the Derivation of Generic Cleanup Criteria



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APPENDIX A

SUBJECT: TECHNICAL SUPPORT DOCUMENT: CRITERIA TO ADDRESS DEVELOPMENTAL-REPRODUCTIVE TOXICITY

Developed under:

MCL 324.20120a(4) *…If a hazardous substance poses a risk of both cancer and 1 or more adverse health effects other than cancer, cleanup criteria shall be derived under this section for the most sensitive effect.*

MCL 324.20120b(2) *Site-specific criteria approved under subsection (1) may, as appropriate:*

(b) Alter any value, parameter, or assumption used to calculate generic criteria, with the exception of the risk targets specified in section 20120a(4).

R 299.34(3) *The department may calculate generic cleanup criteria for certain hazardous substances using exposure assumptions other than those shown in the algorithms in these rules if either of the following conditions is satisfied:*

(a) A hazardous substance causes an adverse effect in a sensitive subpopulation that is not adequately protected or represented by the generic exposure assumptions.

(b) The toxicokinetics of a hazardous substance are not best represented by the average daily dose, when accounting for the most sensitive effect.

Key definitions for terms used in this document:

Critical window of exposure: The developmental period when vulnerability to exposures is increased and can result in developmental effects (EPA, 2006a). (Also termed as critical windows of development or windows of vulnerability.)

Developmental toxicity: The occurrence of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. These adverse effects can be manifested in various ways (death of the developing organism, abnormality, altered growth, or functional deficiency) over the lifespan of the organism (EPA, 1991a).

Lifestages: Temporal stages of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures (EPA, 2006a). This term is also defined as a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth (http://www2.epa.gov/children).

Process Document: Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria (MDEQ, 2015b)

Reproductive toxicity: The occurrence of biologically adverse effects on the reproductive systems of females or males that might result from exposure to harmful substances in the environment. The toxicity may be expressed as alteration to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but not be limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems (EPA 1996a). ***This Technical Support Document and the associated Process Document is intended to address reproductive effects that occur after early-life exposures (from preconception through adolescence).***

Introduction

This Technical Support Document (TSD) presents supporting information for the following document: Process to Address Developmental and/or Reproductive Toxicity in the Derivation of Generic Cleanup Criteria (Process Document). Together, these documents fulfill recommendations of the Criteria Stakeholder Advisory Group (CSA) that convened in 2014 to address updates to the Part 201 Generic Cleanup Criteria (CSA, 2014).

The generic cleanup criterion is required to be protective of the most sensitive health endpoint for the hazardous substance and exposure pathway. Evaluation of potential DR toxicity is essential to make sure that the generic cleanup criteria achieve this requirement. The CSA and the MDEQ have identified a Toxicity Value Decision Framework (MDEQ, 2015a) that RRD will use in determining the best available toxicity values for calculating cleanup criteria as identified in the Process Document.

Early-life receptors (e.g, child, pregnant woman and her fetus) are not a subpopulation, but a lifestage that occurs for the entire population. Although most chemicals have very limited or no data associated with early-life exposure, more focus at the national and international levels on adverse effects from exposures during these lifestages has occurred since the 1990s (EPA, 2006a; WHO, 2011). Early-life receptors have distinct vulnerability to environmental chemicals, compared to adult receptors, due to different exposures and for some chemicals, unique sensitivity to adverse effects. Early-life exposures may result in health effects that manifest either in early-life or in adulthood. There is a growing body of research on developmental origins of adult health and disease that includes exposures to chemicals, as well as other stressors such as nutritional imbalance (Aagaard-Tillery *et al.*, 2008; Barker *et al.*, 2002; Barker, 2012; Byrne and Phillips, 2000; Calkins and Devaskar, 2011; Faulk and Dolinoy, 2011; Fox *et al.*, 2012; Gluckman *et al.*, 2006; Grandjean *et al.*, 2015; Heindel *et al.*, 2015; McMillen *et al.*, 2008; Power *et al.*, 2013; Robinson, 2001). A risk assessment for environmental health effects in children includes information on exposures at each stage of development and on a broad range of outcomes, provided data are available.

The EPA and World Health Organization (WHO) recommend integration of toxicity and exposure at various early lifestages, but have not yet provided sufficient guidance on how to use

existing data for this approach (EPA, 2006a, 2014a, 2014c; WHO, 2006; WHO 2011). EPA's *Risk Assessment Guidance for Superfund* (RAGS) and soil screening guidance documents (EPA, 1989, 1991, 1996a, 1996b, 2002c) contain specific language to account for sensitive subpopulations or children specifically.

The EPA Regional Screening Levels (RSLs) (EPA, 2015a) for noncarcinogenic hazardous substances for residential drinking water, soil, and ambient air use a child receptor (ages 0-6 years). EPA uses a child receptor for the residential RSLs for all hazardous substances to account for the child's increased exposure. Since EPA does not treat chemicals with DR toxicity differently from other chemicals, the associated guidance does not include a separate process for incorporating DR toxicity information to developing health risk-based screening levels or criteria. Although the RSL guide specifies the equations for deriving RSLs for chemicals with mutagenic effects, there are no similar equations specific to noncancer DR endpoints since a child receptor is already used for noncancer endpoints for residential land use.

In the past, risk assessment had been typically based on adult toxicity and exposure data. Most EPA guidance now includes early-life exposures either explicitly, by requiring consideration of children or early-life exposures (EPA, 1991a, 1995a, 2006a, 2006b, 2006c, 2014; FQPA, 1996; EPA R9, 2015), or implicitly, by addressing susceptible subpopulations and/or early lifestages (EPA, 1989, 2002b, 2014a, 2014c). The CSA final report (CSA, 2014) recommends consideration of EPA guidance when developing generic cleanup criteria. The CSA specifically identified the *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA, 2014c) (2014 Framework) as a document to consider for Generic Criteria updates. The 2014 Framework identifies the EPA resources listed below for considering early-life toxicity and exposures. **It is recommended that risk assessors refer to the EPA resources, including those listed below, when identifying Tier 1-3 and setting Tier 4 values for DR toxicity:**

1. *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991a) explains how "to assess the risks for developmental toxicity from exposure to environmental agents." Manifestations of developmental toxicity include altered survival, structure, growth; and functional deficits. This document provides considerations for evaluating predominantly prenatal developmental toxicity studies and, to a lesser extent, considerations for exposure assessment.
2. *Guidelines for Reproductive Toxicity Risk Assessment* (EPA, 1996a) "provides guidance for assessing the effects of environmental agents that might adversely affect human health, including the reproductive system." However, this document does not include how risk assessment should be conducted for these agents.
3. *A Framework for Assessing Health Risks of Environmental Exposures in Children* (EPA, 2006a) is a conceptual overview of considerations for evaluating early-life exposures and subsequent outcomes. Although not a step-by-step process document, it provides a list of questions to consider with each step of the risk assessment process, many of which are specific to developmental toxicants and early-life exposures. These questions may be appropriate to consider in evaluating potential DR toxicants. However, some

questions are only applicable for chemicals with robust datasets or in circumstances where additional studies will be conducted.

4. *Guide to Considering Children's Health when Developing EPA Actions: Implementing Executive Order 13045 and EPA's Policy on Evaluating Health Risks to Children* (EPA, 2006c) (2006 Rulemaking Guide) includes guidance for EPA rulemaking and other policy development that involve human health risks and how to comply with requirements for children's health considerations. The 2006 Rulemaking Guide describes a broad range of early-life, prenatal and postnatal exposures including:
    a) Parental exposure prior to conception
    b) Maternal exposures during pregnancy
    c) Exposures during infancy and childhood
5. The 2008 edition of the *Child-Specific Exposure Factors Handbook* (CSEFH) (EPA, 2008) focused on child's exposure data for many exposure pathways. Significant amounts of comprehensive data regarding exposure during early lifestages are available in the most recent *Exposure Factors Handbook* (EFH) (EPA, 2011a), including data from the CSEFH.
6. *Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology* (EPA, 2014a) describes evaluation of adverse outcomes with various predictive tools including high throughput *in vitro* screening of chemicals' toxicity; determining differing susceptibilities including age, health status and genetics; and developing various computer and biological models predicting kinetic and/or dynamic toxicological processes. (In its final report, the CSA recognized that toxicity studies are evolving with these high throughput methods and other predictive tools [MDEQ, 2014].) Many of these emerging risk assessment tools are likely to aid the assessment of potential developmental toxicants.

The National Academy of Science, National Research Council (NAS/NRC) has advisory documents related to EPA risk assessments that provide advice for accounting for early-life exposures. In its final report (MDEQ, 2014), the CSA recommended consideration of the 2014 NAS/NRC Review of EPA's Integrated Risk Information System (IRIS) Process (NRC, 2014). The NAS/NRC document recommends that EPA continue developing a systematic review process for chemical toxicity evaluations with evidence integration being a key outcome. Although the document is not focused on DR toxicity, it does consider developmental and reproductive endpoints as key components of the chemical review process.

The WHO develops Environmental Health Criteria (EHC) documents that include chemical-specific evaluations and methodologies to assess chemical risks. Early DR toxicity related EHC documents focused on testing methods for early-life susceptibilities (IPCS 1984, 1986). The more recent WHO documents provide general guidance to assess health risks to children from multiple stressors (IPCS, 2006; WHO, 2011).

The Agency for Toxic Substances and Disease Registry (ATSDR) addresses health risks to children within many of their evaluations and when setting MRLs, although guidance specific to addressing chemicals with DR toxic effects is not available at this time.

Many state agencies have established special measures to address child and other early-life susceptibility by using a child receptor in calculating residential cleanup levels. Other examples of state agencies that have specifically addressed early-life exposures include:

1. Minnesota has developed short-term drinking water health reference levels for chemicals with developmental effects; [http://www.health.state.mn.us/divs/eh/risk/rules/water/index.html]
2. Massachusetts has developed immediate and urgent response action levels for trichloroethylene (TCE) based on developmental toxicity (fetal cardiac malformations). [http://www.mass.gov/eea/docs/dep/cleanup/laws/tcestat.pdf; http://www.mass.gov/eea/docs/dep/cleanup/laws/tcevalsm.pdf] Massachusetts also addresses greater exposure to air pollutants for children by using adjustment factors until a more specific approach is developed;
3. California has modified toxicity values to address exposure of school children; and [http://oehha.ca.gov/public_info/public/kids/]
4. Oregon has included breastmilk exposure as part of the risk assessment for polychlorinated biphenyls (PCBs), based on developmental endpoints. [http://www.deq.state.or.us/lq/pubs/docs/cu/HumanHealthRiskAssessmentGuidance.pdf]

The CEHS and TSG note that EPA and many other states address the increased exposure for children by using a child receptor as the default residential receptor for all chemicals, including those chemicals lacking information on developmental toxicity. For most chemicals, information on developmental toxicity is not available and using a child receptor only for identified developmental toxicants could be a disincentive for generating and synthesizing this type of information. Additionally, there is a growing body of literature on the developmental origins of adult disease that includes early-life exposures to environmental chemicals (Grandjean *et al*., 2015; Heindel *et al.*, 2015). Increased toxicity can occur from increased exposure alone, and does not require increased sensitivity to adverse effects. It is well documented that young children have increased exposure to most environmental media. Adult exposure assumptions contribute more than 80% of the averaging time for some of the age-adjusted receptors, and as a result, do not adequately address the increased exposure during early life. As additional data, guidance, and other changes in risk assessment approaches become available, reconsideration of the child as the default receptor for residential land use should be part of any future MDEQ criteria updates.

Identifying Hazardous Substances with DR Toxicity

Hazard identification involves determining if a hazardous substance can cause adverse health effects in humans and what those effects might be (EPA, 2006c). The simplest way to identify if a hazardous substance has DR toxicity is to determine if the endpoint or critical effect for an existing toxicity value is from dosing or exposure during an early-life stage.

Per the CSA recommendations (CSA, 2014), the MDEQ-RRD generates toxicity values based on the Toxicity Value Decision Framework (MDEQ, 2015a) as outlined in the Process

Document. **If a previously identified noncancer toxicity value is not based on a DR endpoint or critical effect, evidence should be assessed to determine if the hazardous substance has DR effects.** This includes determining whether the EPA, ATSDR, WHO, European Union, Canada, or other states have a toxicity value based on DR endpoints or have listed the chemical as a DR toxicant and reviewing the published literature. **A literature search strategy specific to DR toxicity may need to be developed to ensure that relevant noncancer toxicity values and/or studies are located and evaluated.**

Hazard identification typically is based on animal toxicity testing or, in some cases, human epidemiology studies. Most animal toxicity tests do not provide information on developmental toxicity as they are conducted on adult animals. A limited number of chemicals have been evaluated with animal toxicity testing protocols that provide information on DR adverse effects. Most of these testing protocols are focused on prenatal and/or early postnatal (including lactation) exposures. Experimental animal studies of exposure during the juvenile period are rare. Only multigenerational reproductive testing protocols include exposures from prenatal through the post-weaning lifestages of the offspring. These studies are focused on reproductive success of the parental generation and offspring generation(s), with only gross findings typically reported for other organs or systems. Therefore, there is a paucity of toxicity information for exposures from post-weaning to sexual maturity, especially for non-reproductive, developmental endpoints (EPA, 2002a; EPA, 2006a). However, due in part to the Children's Health Centers established by the National Institute of Environmental Health Sciences and the EPA [http://epa.gov/ncer/childrenscenters/], there has recently been an increase in the number of developmental toxicity studies, some of which include cohorts of children. Some studies are evaluating exposures over more than one lifestage, thus it is anticipated that this new research will inform the risk assessment process for DR toxicants.

Developmental effects in animal models may demonstrate a similar or different pattern of developmental perturbation than those seen in humans for the same chemical or class of chemicals. There is usually at least one species that mimics the adverse effect observed in humans, but other species may elicit another of the four manifestations (i.e., death, structural abnormalities, growth alterations, and functional deficits) of developmental toxicity in the same organ or system. Every species may not react the same due to species-specific characteristics in critical periods, differences in timing of exposure, metabolism, developmental patterns, placentation, or mechanism of action (EPA, 1991a). There is no simple temporal comparison across species which varies by organ system and there is not any one laboratory species most similar to humans for developmental effects (Felter *et al*, 2014).

There are some hazardous substances that have sufficient epidemiological data to determine hazard and, in a subset of these chemicals, dose-response. Most of these data are related to occupational (i.e., adults only) exposures. There are some cohorts that include exposures during pregnancy and fewer that include childhood exposures. Study power is crucial to the appropriate interpretation of epidemiological data; these studies typically require thousands of participants to reveal a modest increase in risk. Confidence in findings requires careful control of bias as well as other risk factors, effect modifiers, and confounders (EPA, 1991a). Note that

women's pre-pregnancy/lactation exposure to bioaccumulative, DR toxicants (e.g., PCBs, dioxin-like chemicals, mercury) can extend to the developing fetus and child as a result of placental transfer and breast milk contamination, even after exposure to the mother has terminated (Baccarelli *et al*, 2008; EPA, 2012; Oregon DEQ, 2010).

Prenatal or lactational exposures that result in developmental adverse effects may also show minimal maternal toxicity at the same dose. Adverse developmental effects should not be automatically discounted as secondary to maternal toxicity. At doses causing excessive maternal toxicity, an evaluation of developmental effects may be more difficult. Even if developmental effects are secondary to maternal toxicity, the maternal effects may be mild and/or reversible, but the developmental effects on the offspring are likely permanent (EPA, 1991a). If there are maternal effects at a lower dose than that observed with adverse effects in the offspring, an evaluation of the dose/response for the pregnant female receptor is necessary as compared to other nondevelopmental adverse effects. A pregnant female receptor may be more sensitive than another adult receptor (EPA, 1991a).

Hazard identification can include information on a chemical that indicates that DR toxicity may be a concern, but there is not sufficient dose-response data or other information to generate a DR reference value at the time the chemical is evaluated. **This type of information should be included in the chemical's file to: 1) document criterion is protective of the most sensitive effect; 2) consider appropriate application of extrapolation factors (e.g., data-derived extrapolation factors [DDEFs] or uncertainty factors [UFs]); 3) identify appropriate compliance considerations (e.g., media concentration averaging over time); and 4) establish priority for future updates of cleanup criteria.** Newer high-throughput toxicity testing may also allow better prioritization of chemicals for evaluation of DR toxicity.

Determining the Appropriate Toxicity Value

Dose-response analysis evaluates the quantitative relationship between dose and toxicological responses (EPA, 2006c). These evaluations typically identify threshold exposure levels that are "likely to be without significant harm". In some cases (e.g., lead, arsenic) a threshold may be difficult to determine (EPA, 1991a). Mechanism of action information can help inform the assumption of a threshold. RfVs represent acceptable doses or concentrations and are intended to protect the susceptible individuals in a population from the critical toxic endpoint.

Previously developed noncancer toxicity values (Tier 1-3 sources) based on DR endpoints or effects should be evaluated. Tier 4 derivation of a DR toxicity value will only be necessary if there is not a DR toxicity value from the preferred Tier 1-3 sources and/or if newer data demonstrates that the hazardous substance exhibits DR toxicity.

The DR RfV is determined by dividing a point of departure (POD) value by appropriate DDEFs or UFs, described below. The POD is often the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) found in an animal study, but, in certain circumstances, the Benchmark Dose (BMD) or Benchmark Concentration (BMC) approach may

be applied. Regardless of the source, the POD represents the dose below which no or negligible DR effects are expected to be observed.

Once a NOAEL/LOAEL or BMD/BMC is identified, risk assessors determine appropriate extrapolation factors (e.g., DDEFs, UFs) (EPA, 2014d) for applying the study derived dose for human health risk. Considerations for appropriate DDEFs include:

1. Variability in the human receptor population and the study subject population;
2. Information related to toxicokinetic or toxicodynamic differences between the study subjects and the human receptor population including age-specific differences (e.g., physiologically-based pharmacokinetic model [PBPK] or other biological models); and
3. Uncertainties associated with the key study and/or available studies or information.

When there is insufficient information for a hazardous substance to use DDEFs, UFs are used, to derive the RfD, RfC, or MRL. UFs are generally 1, 3, or 10-fold. The UFs account for:

1. Intraspecies (human interindividual) variability (UF_H);
2. Interspecies (animal-to-human) variability (UF_A);
3. Extrapolation of subchronic experimental exposure to chronic "real-life" exposure (UF_S) – this UF may not be necessary for DR toxicants when the adverse effect is related to less-than-chronic exposure;
4. Extrapolation of a LOAEL to a NOAEL(UF_L); and
5. Inadequate or insufficient database – to protect against the probability of certain sensitive adverse effects (UF_D).

Note that UFs do not address differences in *exposure* between an adult and a child. The derivation of criteria considers both toxicity and exposure. **Therefore, a nonDR RfV that is lower than a DR RfV for the same chemical may not necessarily result in the most protective criteria if the DR receptor has greater exposure.**

Toxicity assessment will continue to evolve with more in-vitro, high throughput studies that can evaluate chemicals rapidly and provide a better understanding of mechanisms and species differences that affect extrapolation. As more of this information is generated, it will result in less uncertainty and better computer modeling to aid risk assessment. Recognizing these potential evolving alternatives and alternative approaches already in use, risk assessors may determine that another approach is appropriate for establishing whether a hazardous substance has or is likely to have DR effects even when there is not sufficient hazardous substance-specific data to develop a DR RfV. Other approaches to consider include:

1. Combining *in vitro* or *in vivo* screening studies or mechanistic data with dose extrapolation (e.g., PBPK model or other biologically-based model);
2. Using hazardous substance(s) with similar structure and toxicity characteristics as a surrogate. Use the surrogate chemical's dose-response data with molar adjustment or another between-chemical extrapolation approach to predict a POD (e.g., read across, relative potency factors);

3. Other approaches as determined appropriate by the MDEQ; or
4. Applying a DDEF or database gap uncertainty factor (UF_D) to the nonDR RfV to protect for DR toxicity until sufficient dose-response data is available. **An appropriate DDEF or UF_D should be used if the other approaches are not available or plausible.**

Ideally, dose-response evaluations consider if chemical-specific information is available regarding differential toxicokinetics or other biological influences that may impact developmental receptors. As an example, a PBPK model can account for different toxicokinetics between the animal model used in the toxicity study and the human child receptor. Toxicokinetic considerations should be appropriate for the lifestage(s) assessed for the DR endpoint and receptor. Validated PBPK models can provide a better estimate of the intake dose required to yield the tissue dose associated with the critical endpoint, thereby decreasing uncertainty in the assessment (i.e., may use a DDEF).

For some chemicals, it is appropriate to use other acceptable health protective chemical standards or concentrations in lieu of a DR RfV (e.g., Centers for Disease Control and Prevention Blood Lead Level goal, National Ambient Air Quality Standards). In addition, there may be models that are used as part of the dose-response assessment (e.g., biologically-based dose-response models) or for both the dose-response and exposure assessment (e.g., the EPA lead models).

Dose-response assessment for the inhalation pathway requires special consideration. The EPA (2009) recommends that risk assessors use the concentration of the chemical in air (e.g., milligram per cubic meter or mg/m^3) rather than a dose based on inhalation rate and body weight (e.g., milligram per kilogram per day or mg/kg-day) as the exposure metric in equations for calculating risk-based concentrations, in order to be more consistent with the EPA dosimetry guidance (1994). The EPA (2009) clarifies that IURFs and RfCs used in the risk-based concentration equations are for continuous (24 hours per day [hr/d]) exposure. If the exposure scenario of interest is less than 24 hr/d, the exposure time in hr/d should be used in the equations and the averaging time should be in units of hours. POD concentrations from animal studies (e.g., 6 hr/d, 5 days per week) are typically adjusted for continual exposures (i.e., 24 hr/d, 7 days per week) as a default procedure for repeated-dose exposure studies. For most DR toxicants with a shorter critical window of exposure, however, this continual exposure adjustment may not be appropriate. Both the inhalation unit risk factor (IURF) and reference concentration (RfC) derivations rely on the extrapolation of experimental concentrations to human equivalent concentrations via the dosimetry guidance. Human equivalent concentrations are determined by applying a dosimetric adjustment factor to the POD concentration from an animal study. The dosimetric adjustment factor is typically based on ratios of animal and adult human physiologic parameters, for particles and gases.

The accounting for potential DR effects in dose-response assessment for the inhalation exposure pathway may be best demonstrated by way of example. TCE has an RfC of 2 micrograms per cubic meter ($\mu g/m^3$) (EPA, 2011b). The EPA does not assign ATs to RfCs, and they do not typically explicitly address concerns for short-term excursions above the RfC.

However, in this particular case, one of the two key studies supporting the RfC is a developmental study (Johnson *et al*., 2003) in which drinking water exposures to pregnant rats during gestation days 1-22 resulted in an increase in cardiac malformations in the offspring. EPA (2011b) derived the RfC from this developmental study using a $BMDL_{01}$ for the POD and a composite UF = 10, consisting of an UF_A= 3 for toxicodynamic uncertainty and UF_H= 3 for possible toxicodynamic differences in sensitive humans. Note that a UF_S= 1 was assigned. A higher UF_S was not utilized in deriving the RfC for protection for lifetime exposures, even though the exposure period was only on gestation days 1-22, because, "…the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect" (EPA, 2011b). EPA (2011c) further explains that, "For some reproductive and developmental effects, chronic exposure is that which covers a specific window of exposure that is relevant for eliciting the effect, and subchronic exposure would correspond to an exposure that is notably less than the full window of exposure." EPA (2014b) provides further guidance and information on TCE, including, "In most cases, it is assumed that a single exposure at any of several developmental stages may be sufficient to produce an adverse developmental effect, but the RfC for a single exposure hasn't been determined yet by EPA."

The MDEQ Air Quality Division has established an initial threshold screening level for TCE that is consistent with the EPA RfC, and has applied a 24-hour averaging time (AT), as it is prudent to ensure protection from potential developmental effects as demonstrated in the study by Johnson *et al*. (2003). It is recommended that MDEQ cleanup criteria for the TCE inhalation pathway likewise focus on the acute dose-response and exposure potential by ensuring that airborne exposures do not exceed 2 µg/m^3 with a 24-hour AT. **This can be accomplished by adjustments to the AT, exposure duration (ED), and exposure frequency (EF) in the Part 201 algorithms that reflect a 24-hour period, and by ensuring that measurements and modeling of potential exposure levels have accounted for peak 24-hour concentrations rather than just long-term average concentrations.**

Evaluating Exposures for Early-life Receptors

Exposure assessment estimates the levels of the hazardous substances that come in contact with children and other populations of concern (EPA, 2006c). Most DR toxicity studies evaluate effects on the developing fetus. The pregnant woman is the receptor of interest to protect for adverse effects on the developing fetus. Current guidance and information indicates that the young child is also susceptible to DR toxicity, although the database for toxicity studies during this lifestage is not robust. **Based on currently available information for both toxicity and exposure, the pregnant woman and the young child are the key receptors for DR toxicants, unless there is chemical-specific information that a different critical window of exposure is appropriate.** As an example, hazardous substances that are bioaccumulative will build up over time in the receptor. For these bioaccumulative hazardous substances, the woman's body burden prior to pregnancy contributes more of an impact to the developing fetus than her exposure during pregnancy (EPA, 2012). Exposure assumptions should be consistent with the dose-response assessment that accounts for this bioaccumulation. **In most cases, although the child will still be the appropriate receptor for residential land use, the pregnant woman should also be evaluated for any land use and woman of child-bearing**

age for bioaccumulative DR toxicants. Evaluation of lactational exposure may also be important for many bioaccumulative DR toxicants (Oregon DEQ, 2010).

The available guidance (EPA, 1991a, 2006a; WHO, 2006) and published literature identify multiple lifestages that need to be addressed. The timing of chemical exposure may have different consequences to children's health. There are differing windows of sensitivity for the same chemical and dose during different periods of development. Windows of early-life susceptibility may be broad and can extend from preconception through the end of adolescence (EPA, 2006a; WHO, 2011). There may be shorter critical windows for certain organs or organ systems given a specific chemical and/or adverse outcome. **When the "critical window of exposure" is established or identified for a chemical, the exposure assumptions should be modified accordingly.**

It is known that a developing fetus is more susceptible to certain chemicals. There are sufficient data for many hazardous substances demonstrating that adverse endpoints can result after a single day or shorter exposure during prenatal development (EPA, 1991a; EPA,1992; EPA, 1996a; EPA,1998). Mortality, structural or functional abnormalities (terata) are adverse effects that are most likely to occur from an acute or single event fetal exposure (EPA, 2002a; EPA, 2015c; Barone, 2016). Structural or functional abnormalities that require consideration of a single event include developmental neurotoxicity (EPA, 1998). **Following EPA guidance (EPA, 1991a; EPA, 1992; EPA, 1996a; EPA, 2006a), if the specific time frame of exposure for effects is unknown, then a single day or event should be assumed as the critical window for prenatal exposures with adverse effects including mortality, structural or functional abnormalities (EPA, 2015c; Barone, 2016). An average exposure during the full-term of the pregnancy (280 days) can be considered for prenatal exposures with adverse effects that result in only altered growth (e.g., reduced birth weight, delayed ossification) without structural or functional abnormalities (EPA, 2015c; Barone, 2016).**

Although there are clear examples of infant or childhood susceptibility (e.g., nitrate/nitrite, lead), the database of hazardous substances assessed for adverse effects during infancy or childhood is not robust. As a result, there is not sufficient information to inform whether a narrow or broad critical window is appropriate for early childhood exposures. There is no clear guidance from EPA except that the RSLs are based on a young child exposure duration (0-6 years), although this approach is used without consideration of DR toxicity. **Until additional information or guidance becomes available, the EPA approach of averaging child exposure over 0-6 years of age is appropriate for residential exposures and hazardous substances with DR toxicity, unless there is chemical-specific information for a different critical window.**

If the critical effect of a hazardous substance has sufficient data to determine that the specific critical window of exposure in humans is different than averaging over 0-6 years for the young child or a single day for the pregnant female, then that information may be used to develop age-specific exposure assumptions for the specific critical window of exposure sensitivity. In most cases, there will not be sufficient information to eliminate concerns for potential susceptibility of other early-life stages for the chemical. For single day, acute, or other short-term exposures,

assumptions for average exposure should be evaluated for adequate health protection. In some instances, a higher end assumption may be appropriate, while still balancing the exposure assumptions to assure the overall assessment is relevant and reasonable for the acute or short-term exposure under consideration. **If exposure assumptions appropriate to a shorter-term critical window documented for a chemical will result in more protective criteria, then those assumptions should be used with the corresponding dose/response assessment.**

The EPA RSLs (EPA, 2015a) for residential land use are derived based on a child receptor since children are more susceptible to toxic effects due to greater exposure per unit body mass. As such, EPA has not developed a special process for RSLs specific to DR hazardous substances using a child receptor. In the case of pregnant female workers, the EPA does not have general guidance for addressing the risk of exposure of this sensitive subpopulation to DR toxicants. However, the EPA has made recommendations to consider the first trimester of pregnancy for TCE inhalation exposure to protect for fetal cardiac malformations (EPA R9, 2014) and the recently released EPA guidance (2015b) for vapor intrusion also supports the evaluation of short-term and acute effects with trichloroethylene as an example. Other EPA programs (e.g., Federal Insecticide, Fungicide, and Rodenticide Act; Safe Drinking Water Act, Clean Air Act) are also addressing risks to early-life exposures.

The equations in Appendix B are similar to those used for deriving the generic cleanup values for other noncarcinogenic endpoints and are used for deriving the generic DR cleanup values. The exposure assumptions used in the equations need to match the appropriate DR receptor (e.g., child receptor or the pregnant female receptor), as appropriate for the hazardous substance and DR RfV.

Table 1. Exposure Assumptions for DR Cleanup Values[a]

Exposure Assumptions	Residential – Child	Residential – Pregnant or Child-bearing Age Woman Single Event DR Toxicants	Residential – Pregnant or Child-bearing Age Woman[b] Full-Term DR Toxicants	Nonresidential Pregnant or Child-bearing Age Female Worker Single Event DR Toxicants	Nonresidential Pregnant or Child-bearing Age Female Worker[b] Full-Term DR Toxicants
Averaging time	2,190 days	1 day[c]	280 days	1 day[c]	280 days
Exposure duration	6 years	1 day[c]	0.767 year	1 day[c]	0.767 year
Ingestion and inhalation exposure frequency	350 days/year	1 day/day[c]	268.5 days/year	1 day/day[c]	183 days/year
Dermal exposure frequency	275 days/year	1 day/day[c]	268.5 days/year	1 day/day[c]	
Drinking water ingestion rate	0.78 L/day	1.8 L/day	1.8 L/day	0.9 L/day	0.9 L/day
Soil ingestion rate	179 mg/day	100 mg/day	100 mg/day	100 mg/day	100 mg/day
Body weight All trimesters 1st trimester 2nd trimester 3rd trimester	15 kg	 75 kg 76 kg 73 kg 80 kg	 75 kg 76 kg 73 kg 80 kg	 75 kg 76 kg 73 kg 80 kg	 75 kg 76 kg 73 kg 80 kg
Dermal exposure events	1 event/day	1 event/day	1 event/day	1 event/day	1 event/day
Skin surface area	2,400 cm^2	3,100 cm^2	3,100 cm^2	3,100 cm^2	3,100 cm^2
Skin area-weighted soil adherence factor	0.3 mg/cm^2	0.07 mg/cm^2	0.07 mg/cm^2	0.2 mg/cm^2 [c]	0.07 mg/cm^2

[a] Values based on Syracuse Research Corporation (SRC, 2015) recommendations, unless noted with [c] footnote. See SRC technical support documents for details. These values are to be used unless chemical-specific information is available that a different critical window of exposure is appropriate for a hazardous substance.

[b] For bioaccumulative hazardous substances, in addition to the child for the residential receptor, evaluate age-adjusted residential values and nonresidential worker values appropriate for nonDR toxicity for women of child-bearing age unless chemical-specific information indicates alternate exposure assumptions are appropriate.

[c] See CEHS recommendation below for value instead of SRC recommended value.

CEHS Recommendation for Pregnant or Child-bearing Age Woman Receptor

RRD requested that the Children's Environmental Health Subcommittee (CEHS) of the Toxics Steering Group evaluate the following exposure assumption recommendations for pregnant or child-bearing age workers for hazardous substances with reference values for developmental toxicity.

AT and ED are typically expressed with the following units:

- AT - days (days/year * years)
- ED - years

These parameters are set equivalent to a single day/event to account for short critical windows for developmental toxicity related to prenatal exposures with adverse effects including mortality or structural or functional abnormalities. Since this single day exposure is very different from the typical chronic exposure scenario expressed in years, the pregnant worker equations requires a change in the values and units for these parameters to a single day.

EF is typically expressed in days/year. Since the exposure is a single day, the exposure frequency is not necessary for the calculation for the pregnant worker and, optimally, could be omitted from the equation. If EF is included in the equation for the pregnant worker to be consistent with the generic equations, the value and unit should be 1 day/day. This will be consistent with the value and unit of 1 day for ED.

For the skin adherence factor (AF) for soil direct contact and the pregnant nonresidential receptor (i.e., a worker), SRC recommended the AF for residential adult soil contact activities AF (e.g., adult gardeners, farmers) rather than the nonresidential worker AF (e.g., construction workers, utility workers, equipment operators). The CEHS recommends using the same AF that is used for the generic worker be used for the pregnant nonresidential worker receptor. It is reasonable to assume a pregnant worker will have the same exposure potential for soil adherence as the generic worker, especially based on the requirements of the Pregnancy Discrimination Act of 1978 (PDA). The PDA forbids discrimination based on pregnancy including changing job assignments even if "based on fears of danger to the employee or her fetus, fears of potential tort liability, assumptions and stereotypes about the employment characteristics of pregnant women such as their turnover rate, or customer preference."[2]

Calculating Generic DR Health-based Values

This step uses the appropriate exposure pathway algorithm to combine the DR toxicity value(s) with the DR receptor exposure assumptions to calculate DR noncancer health-based value(s). The algorithms for calculating the noncancer health-based values for DR toxicants are shown in Appendix B.

[2] US Equal Employment Opportunity Commission Notice 915.003, 2015. Enforcement Guidance: Pregnancy Discrimination and Related Issues. http://www.eeoc.gov/laws/guidance/pregnancy_guidance.cfm#

Since the criteria are required to be protective of the most sensitive effect, calculated values for DR noncancer endpoints are compared to values for cancer and other noncancer endpoints. The lowest calculated value is the final health-based value for the most sensitive effect. In some cases, noncancer values will need to be calculated for both nonDR toxicity and DR toxicity.

Document DR Toxicity Information and Compliance Considerations

Consistent with the CSA recommendation for transparency regarding the basis for generic cleanup criteria, documentation of the DR toxicity evaluation is necessary. Information regarding DR toxicity will be included in the chemical's file to document that the final criterion is protective of the most sensitive effect, to identify appropriate compliance considerations (e.g., averaging media concentrations over time), or to identify that a hazardous substance does not have sufficient information to determine DR RfV and will need to be a priority for future updates of the cleanup criteria.

For DR toxicity, single event prenatal exposures may result in adverse effects including mortality or structural or functional abnormalities. As a result, it is not appropriate to average environmental media concentrations over time to compare to criteria based on these adverse effects. This applies for both residential and nonresidential land use. Although a child receptor is used for generic residential land use, these criteria are also intended to protect for exposure for a pregnant woman. When chemical-specific information indicates that a different critical exposure window is appropriate, that critical exposure window should be the averaging time for environmental media concentrations.

Since peak single event exposures will be the appropriate averaging time for many hazardous substances with DR toxicity, the CEHS evaluated the difference between long-term average and high-end (e.g., 90-95 percentile) intake rates from EFH (EPA, 2011). For most critical intake rates such as drinking water intake, the high-end intake was typically within five times the average intake rate.

The final criterion for the hazardous substance and exposure pathway may be either a cancer or noncancer value. If the final criterion is based on DR toxicity or the calculated DR health-based value is within five times the final criterion, it is important to document the appropriate averaging time or other considerations for the evaluation of environmental media data to compare to the final criterion. This information needs to be clearly identified with the published criterion, such as a footnote to the hazardous substance or criterion, as appropriate.

Documentation should identify the following:

1. If there is insufficient information to determine if the hazardous substance has DR toxicity;
2. If the hazardous substance has been evaluated for DR toxicity, but the final criterion is less than five times a calculated DR health-based value; or

3. If a final criterion is based on DR toxicity or the calculated DR cleanup value is within five times the final criterion, document if averaging environmental media concentrations is appropriate for comparison to the criterion. This may be best accomplished with a footnote for the hazardous substance or the exposure pathway criterion.

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APPENDIX B: Equations for Calculating Cleanup Values for DR Toxicants

Developmental Drinking Water Value

Residential (child):

$$DWV_{dev} = \frac{THQ \times AT_{child} \times RfD_{dev} \times BW_{child} \times RSC_w \times CF}{ED_{child} \times EF_{res} \times IR_{dw,child}}$$

where,

DWV_{dev}	(Drinking water value)	=	chemical-specific, µg/L or ppb
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
RfD_{dev}	(Oral reference dose)	=	chemical-specific, mg/kg-day
BW_{child}	(Body weight)	=	15 kg
RSC_w	(Relative source contribution)	=	0.2 or chemical-specific
CF	(Conversion factor)	=	1000 µg/mg
ED_{child}	(Exposure duration)	=	6 years
EF_{child}	(Exposure frequency)	=	350 days/year
$IR_{dw,\ child}$	(Drinking water ingestion rate)	=	0.78 L/day

Residential (pregnant woman):

$$DWV_{dev} = \frac{THQ \times AT_{preg} \times RfD_{dev} \times BW_{preg} \times RSC_w \times CF}{ED_{preg} \times EF_{dev} \times IR_{dw,\ preg}}$$

where,

DWV_{dev}	(Drinking water value)	=	chemical-specific, µg/L or ppb
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
RfD_{dev}	(Oral reference dose)	=	chemical-specific, mg/kg-day
BW_{preg}	(Body weight, pregnant resident)	=	75 kg
RSC_w	(Relative source contribution)	=	0.2 or chemical-specific
CF	(Conversion factor)	=	1,000 µg/mg
$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{preg,FT}$	(Exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{preg,SE}$	(Exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific
$IR_{dw,\ preg}$	(Drinking water ingestion rate, pregnant resident)	=	1.8 L/day

Nonresidential (pregnant worker):

$$DWV_{dev} = \frac{THQ \times AT_{dev} \times RfD_{dev} \times BW_{dev} \times RSC_w \times CF}{ED_{dev} \times EF_{dev} \times IR_{dw,dev}}$$

where,

DWV_{dev}	(Drinking water value)	=	chemical-specific, µg/L or ppb
THQ	(Target hazard quotient)	=	1
$AT_{dev,FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev,SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
RfD_{dev}	(Oral reference dose, developmental)	=	chemical-specific, mg/kg-day
BW_{dev}	(Body weight, pregnant worker)	=	75 kg
RSC_w	(Relative source contribution)	=	0.2 or chemical-specific
CF	(Conversion factor)	=	1,000 µg/mg
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical specific
$EF_{dev,FT}$	(Exposure frequency, pregnant worker, full-term pregnancy)	=	183 days/year or chemical specific
$EF_{dev,SE}$	(Exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical specific
$IR_{dw,\ dev}$	(Drinking water ingestion rate)	=	0.9 L/day

Developmental Direct Contact Value

Residential (child):

$$DCV_{dev} = \frac{THQ \times AT_{child} \times BW_{child} \times RSC_s \times CF}{ED_{child} \times [(\frac{1}{RfD_{o,dev}} \times EF_{i,res} \times IR_{s,child} \times AE_i) + (\frac{1}{RfD_{d,dev}} \times EF_{d,res} \times SA_{child} \times EV \times AF_{child} \times AE_d)]}$$

where,

DCV_{dev}	(Direct contact value)	=	chemical-specific, µg/kg or ppb)
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
BW_{child}	(Body weight)	=	15 kg
RSC_s	(Relative source contribution for soil)	=	1 or chemical-specific
CF	(Conversion factor)	=	1E+9 µg/kg
ED_{child}	(Exposure duration)	=	6 years
$RfD_{o,dev}$	(Oral reference dose, developmental)	=	chemical-specific mg/kg-day
$EF_{i,res}$	(Ingestion exposure frequency)	=	350 days/year
$IR_{s,child}$	(Soil ingestion rate)	=	179 mg/day
AE_i	(Ingestion absorption efficiency)	=	chemical-specific or as specified by chemical category

$RfD_{d,dev}$	(Dermal reference dose)	=	chemical-specific mg/kg-day
$EF_{d,res}$	(Dermal exposure frequency)	=	275 days/year
SA_{child}	(Skin surface area)	=	2,400 cm^2
EV	(Event frequency)	=	1 event/day
AF_{child}	(Soil adherence factor)	=	0.3 mg/cm^2-event
AE_d	(Dermal absorption efficiency)	=	chemical-specific or as specified by chemical category

Residential (pregnant woman):

$$DCV_{dev} = \frac{THQ \times AT_{preg} \times BW_{preg} \times RSC_s \times CF}{ED_{preg} \times [(\frac{1}{RfD_{o,dev}} \times EF_{i,preg} \times IR_{s,preg} \times AE_i) + (\frac{1}{RfD_{d,dev}} \times EF_{d,preg} \times SA_{preg} \times EV \times AF_{preg} \times AE_d)]}$$

where,

DCV_{dev}	(Direct contact value)	=	chemical-specific, µg/kg or ppb)
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
BW_{preg}	(Body weight, pregnant resident)	=	75 kg
RSC_s	(Relative source contribution for soil)	=	1 or chemical-specific
CF	(Conversion factor)	=	1E+9 µg/kg
$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$RfD_{o,dev}$	(Oral reference dose)	=	chemical-specific, mg/kg-day
$EF_{i,preg,FT}$	(Ingestion exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{i,preg,SE}$	(Ingestion exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific
$IR_{s,preg,FT}$	(Soil ingestion rate)	=	89 mg/day
$IR_{s,preg,SE}$	(Soil ingestion rate)	=	100 mg/day
AE_i	(Ingestion absorption efficiency)	=	chemical-specific or as specified by chemical category
$RfD_{d,dev}$	(Dermal reference dose)	=	chemical-specific, mg/kg-day
$EF_{d,preg,FT}$	(Dermal exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{d,preg,SE}$	(Dermal exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific
SA_{preg}	(Skin surface area, pregnant resident)	=	5,500 cm^2
EV	(Event frequency)	=	1 event/day

AF_{preg}	(Soil adherence factor)	=	0.07 mg/cm^2-event
AE_d	(Dermal absorption efficiency)	=	chemical-specific or as specified by chemical category

Nonresidential (pregnant worker):

$$DCV_{nc} = \frac{THQ \times AT_{dev} \times BW_{dev} \times RSC_s \times CF}{ED_{dev} \times \left[\left(\frac{1}{RfD_{o,dev}} \times EF_{i,dev} \times IR_{s,dev} \times AE_i \right) + \left(\frac{1}{RfD_{d,dev}} \times EF_{d,dev} \times SA_{dev} \times EV \times AF_{dev} \times AE_d \right) \right]}$$

where,

DCV_{dev}	(Direct contact value)	=	chemical-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
$AT_{dev, FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev, SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
BW_{dev}	(Body weight, pregnant worker)	=	75 kg
RSC_s	(Relative source contribution)	=	1 or chemical-specific
CF	(Conversion factor)	=	1E+9 µg/kg
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
$RfD_{o,dev}$	(Oral reference dose, developmental)	=	chemical-specific, mg/kg-day
$EF_{i,dev,FT}$	(Ingestion exposure frequency, pregnant worker, full-term pregnancy)	=	183 days/year or chemical-specific
$EF_{i,dev,SE}$	(Ingestion exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical-specific
$IR_{s,dev,FT}$	(Soil ingestion rate, pregnant worker, full-term pregnancy)	=	89 mg/day
$IR_{s,dev,SE}$	(Soil ingestion rate, pregnant worker, single event exposure during pregnancy)	=	100 mg/day
AE_i	(Ingestion absorption efficiency)	=	chemical-specific or as specified by chemical category
$RfD_{d,dev}$	(Dermal reference dose, developmental)	=	chemical-specific, mg/kg-day
$EF_{d,dev,FT}$	(Dermal exposure frequency, pregnant worker)	=	183 days/year or chemical-specific
$EF_{d,dev,SE}$	(Dermal exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical specific
SA_{dev}	(Skin surface area, pregnant worker)	=	3,100 cm^2/day

EV	(Event frequency)	=	1 event/day
AF_{dev}	(Soil adherence factor, pregnant worker)	=	0.2 mg/cm^2-event
AE_d	(Dermal absorption efficiency)	=	chemical-specific or as specified by chemical category

Developmental Acceptable Air Value

Residential (child):

$$AAV_{dev} = \frac{THQ \times AT_{child} \times RfC_{dev} \times RSC}{ED_{child} \times EF_{child}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
ED_{child}	(Exposure duration)	=	6 years
EF_{child}	(Exposure frequency)	=	350 days/year

Residential (pregnant woman):

$$AAV_{dev} = \frac{THQ \times AT_{preg} \times RfC_{dev} \times RSC}{ED_{preg} \times EF_{preg}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{preg,FT}$	(Exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{preg,SE}$	(Exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific

Nonresidential (pregnant worker):

$$AAV_{dev} = \frac{THQ \times AT_{dev} \times RfC_{dev} \times RSC}{ED_{dev} \times EF_{dev}}$$

where,

AAV_{dev}	(Acceptable air value)	=	chemical-specific, µg/m^3
THQ	(Target hazard quotient)	=	1
$AT_{dev,FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev,SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{dev,FT}$	(Exposure frequency, pregnant worker, full-term pregnancy)	=	183 days/year or chemical-specific
$EF_{dev,SE}$	(Exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical-specific

Developmental Volatile Soil Inhalation Value

Residential (child):

$$VSIV_{dev} = \frac{THQ \times AT_{child} \times RfC_{dev} \times RSC}{ED_{child} \times EF_{res} \times \left(\frac{1}{VF_{res}}\right)}$$

where,

$VSIV_{dev}$	(Volatile soil inhalation value for infinite or finite source)	=	chemical- and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
ED_{child}	(Exposure duration)	=	6 years
EF_{res}	(Exposure frequency)	=	350 days/year
VF_{res}	(Volatilization factor for infinite or finite source)	=	chemical- and source size-specific, m^3/kg

Residential (pregnant woman):

$$VSIV_{dev} = \frac{THQ \times AT_{preg} \times RfC_{dev} \times RSC}{ED_{preg} \times EF_{preg} \times \left(\frac{1}{VF_{res}}\right)}$$

where,

$VSIV_{dev}$	(Volatile soil inhalation value for infinite or finite source)	=	chemical and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{preg,FT}$	(Exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{preg,SE}$	(Exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific
VF_{res}	(Volatilization factor for infinite or finite source)	=	chemical and source size-specific, m^3/kg

Nonresidential (pregnant worker):

$$VSIV_{dev} = \frac{THQ \times AT_{dev} \times RfC_{dev} \times RSC}{ED_{dev} \times EF_{dev} \times (1/VF_{dev})}$$

where,

$VSIV_{dev}$	(Volatile soil inhalation value for infinite or finite source)	=	chemical- and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
$AT_{dev,FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev,SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	0.767 year or chemical-specific

$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{dev,FT}$	(Exposure frequency, pregnant worker, full-term pregnancy)	=	183 days/year or chemical-specific
$EF_{dev,SE}$	(Exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical-specific
VF	(Volatilization factor for infinite or finite source)	=	chemical- and source size-specific, m^3/kg

Developmental Particulate Soil Inhalation Value

Residential (child):

$$PSIV_{dev} = \frac{THQ \times AT_{child} \times RfC_{dev} \times RSC}{ED_{child} \times EF_{res} \times \left(\frac{1}{PEF_{dev}}\right)}$$

where,

$PSIV_{dev}$	(Particulate soil inhalation value)	=	chemical- and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
AT_{child}	(Averaging time)	=	2,190 days
RfC_{dev}	(Reference concentration, developmental)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific
ED_{child}	(Exposure duration)	=	6 years
EF_{res}	(Exposure frequency)	=	350 days/year
PEF_{dev}	(Particulate emission factor)	=	source size-specific, m^3/kg

Residential (pregnant woman):

$$PSIV_{dev} = \frac{THQ \times AT_{preg} \times RfC_{dev} \times RSC}{ED_{preg} \times EF_{preg} \times \left(\frac{1}{PEF_{dev}}\right)}$$

where,

$PSIV_{dev}$	(Particulate soil inhalation value)	=	chemical- and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
$AT_{preg,FT}$	(Averaging time, full-term pregnancy)	=	280 days or chemical-specific
$AT_{preg,SE}$	(Averaging time, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration)	=	chemical-specific, µg/m^3
RSC	(Relative source contribution)	=	1 or chemical-specific

$ED_{preg,FT}$	(Exposure duration, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{preg,SE}$	(Exposure duration, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{preg,FT}$	(Exposure frequency, full-term pregnancy)	=	268.5 days/year or chemical-specific
$EF_{preg,SE}$	(Exposure frequency, single event exposure during pregnancy)	=	1 day/day or chemical-specific
PEF_{dev}	(Particulate emission factor)	=	source size-specific, m^3/kg

Nonresidential (pregnant worker):

$$PSIV_{dev} = \frac{THQ \times AT_{dev} \times RfC_{dev} \times RSC}{ED_{dev} \times EF_{dev} \times \left(\frac{1}{PEF_{dev}}\right)}$$

where,

$PSIV_{dev}$	(Particulate soil inhalation value)	=	chemical- and source size-specific, µg/kg or ppb
THQ	(Target hazard quotient)	=	1
$AT_{dev,FT}$	(Averaging time, pregnant worker, full-term pregnancy)	=	280 days or chemical-specific
$AT_{dev,SE}$	(Averaging time, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
RfC_{dev}	(Reference concentration)	=	chemical-specific, $\mu g/m^3$
RSC	(Relative source contribution)	=	1 or chemical-specific
$ED_{dev,FT}$	(Exposure duration, pregnant worker, full-term pregnancy)	=	0.767 year or chemical-specific
$ED_{dev,SE}$	(Exposure duration, pregnant worker, single event exposure during pregnancy)	=	1 day or chemical-specific
$EF_{dev,FT}$	(Exposure frequency, full-term pregnancy)	=	183 days/year or chemical-specific
$EF_{dev,SE}$	(Exposure frequency, pregnant worker, single event exposure during pregnancy)	=	1 day/day or chemical-specific
PEF_{dev}	(Particulate emission factor, pregnant worker)	=	source size-specific, m^3/kg