Final Human Health Risk Assessment Scope of Work

The following scope of services for Intertox, Inc. (Intertox) is based on the task structure of HDR Engineering, Inc.'s (HDR) scope of services, which is included in the prime agreement between HDR and the LOTT Clean Water Alliance (LOTT) for the Reclaimed Water Infiltration Study (RWIS) Phase III, which in turn is referenced by the subcontract between Intertox and HDR.

The task within which Intertox is responsible for providing services is Task 3.1 (Human Health Risk Assessment). This amendment covers risk assessment activities, as described below in Task 3.1.2.

3.1 Human Health Risk Assessment (HHRA)

Objective: For residual chemicals analyzed in LOTT's reclaimed water, assess the impact of adding reclaimed water at current water quality (i.e., Class A) as well as the relative effectiveness of treatment scenarios on reducing risks, to provide scientific data to support decision-making regarding treatment and reclaimed water use.

[Section 3.1.1 (Screening Level Evaluation) not shown, as this is completed.]

3.1.2 Human Health Risk Assessment (HHRA)

Using the subset of COIs identified as warranting further evaluation following groundwater fate and transport modelling, Intertox will conduct a human health risk assessment (HHRA) to assess the potential significance of predicted concentrations of residual chemicals from reclaimed water in domestic and municipal water supply wells, as well as groundwater and surface water. Two approaches will be used:

- Estimated exposure point concentrations will be compared to published drinking water criteria.
- Average daily doses of chemicals of interest resulting from ingestion of or direct dermal contact with water will be estimated per standard U.S. EPA human health risk assessment methodologies, and used to predict noncancer hazards and cancer risks associated with chronic daily exposure.

The approaches that will be applied for each of these are described in further detail below.

Overall, the goals of the HHRA are to:

- Evaluate whether exposure to any of the residual chemicals in recharged groundwater, based on measured or predicted concentrations, could present a significant human health risk via potential pathways of exposure, by (1) comparing concentrations to existing drinking water criteria or action levels and (2) by estimating noncancer hazards and/or cancer risks using existing or derived toxicity reference values and criteria;
- Identify which of the residual chemicals and exposure pathways are likely to contribute most significantly to estimated risks;

- Rank treatment and exposure scenarios based on relative risk estimates;
- Evaluate the potential relevance of findings to chemicals not included in the suite of analyzed compounds;
- Characterize factors that contribute most significantly to uncertainties in the risk characterization; and
- To support risk communication, compare risks associated with predicted exposure to residual chemicals in reclaimed water to other sources of exposure.

The health risk evaluation will apply methodologies from current U.S. EPA and other risk assessment guidance and policies as appropriate**,** for example the following:

- U.S. EPA, 1989. Risk Assessment Guidance for Superfund (RAGS), Volume I. Human Health Evaluation Manual, Part A. Interim Final. Office of Solid Waste and Emergency Response, United States Environmental Protection Agency. Washington, D.C. EPA/540/1-89/002. December.
- U.S. EPA, 1991. Human Health Evaluation Manual, Supplemental Guidance: Standard Default Exposure Parameters. Office of Solid Waste and Emergency Response, United States Environmental Protection Agency. Washington, D.C. June.
- U.S. EPA, 1992. Dermal Exposure Assessment: Principles and Applications. Office of Research and Development, United States Environmental Protection Agency. Washington, D.C. EPA/600/8-91/011B. January.
- U.S. EPA, 1992. Supplemental Guidance to RAGS: Calculating the Concentration Term. Office of Solid Waste and Emergency Response. Washington, D.C. May.
- U.S. EPA, 1996. Soil Screening Guidance. Technical Background Document. Office of Solid Waste and Emergency Response, United States Environmental Protection Agency. Washington, D.C. EPA/540-R-95-128. July.
- U.S. EPA, 2002. A Review of the Reference Dose and Reference Concentration Processes. United States Environmental Protection Agency. Washington, D.C. EPA/630/P-02/002F. December.
- U.S. EPA, 2003. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Technical Support Document. Volume 2: Development of National Bioaccumulation Factors. United States Environmental Protection Agency. Washington, D.C. EPA-822-R-03-030. May.
- U.S. EPA, 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, United States Environmental Protection Agency. Washington, D.C. EPA/630/P-03/001F. March.
- U.S. EPA, 2006. A Framework for Assessing Health Risk of Environmental Exposures to Children. United States Environmental Protection Agency. Washington, D.C. EPA/600/R-05/093F. September.
- U.S. EPA, 2008. Child-Specific Exposure Factors Handbook. United States Environmental Protection Agency. Washington, D.C. EPA/600/R-06/096F. September.
- U.S. EPA, 2009. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Technical Support Document. Volume 3: Development

of Site-Specific Bioaccumulation Factors. United States Environmental Protection Agency. Washington, D.C. EPA-822-R-09-008. September.

- U.S. EPA, 2011. Exposure Factors Handbook. Office of Research and Development, United States Environmental Protection Agency. Washington, D.C. EPA/600/R-090/052F. September.
- U.S. EPA, 2011. Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose. United States Environmental Protection Agency. Washington, D.C. EPA/100/R11/0001.
- U.S. EPA, 2012. Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. Office of Pesticide Programs. United States Environmental Protection Agency. Washington, D.C.
- U.S. EPA, 2012. Benchmark Dose Technical Guidance. United States Environmental Protection Agency. Washington D.C. EPA/100/R-12/001. June.
- U.S. EPA, 2014. Framework for Human Health Risk Assessment to Inform Decision Making. United States Environmental Protection Agency. Washington D.C. EPA/100/R-14/001. April.
- U.S. EPA, 2018. Region 4 Human Health Risk Assessment Supplemental Guidance. United States Environmental Protection Agency. March.
- U.S. EPA, 2019. Guidelines for Exposure Assessment. United States Environmental Protection Agency. Washington, D.C. EPA/100/B-19/001. October.
- U.S. EPA, 2019. Update for Chapter 3 of the Exposure Factors Handbook: Ingestion of Water and Other Select Liquids. United States Environmental Protection Agency. Washington D.C. EPA/600/R-18-259F. February.
- Washington State Department of Ecology. 2007. Model Toxics Control Act Statute and Regulation. Publication No. 94-06. November.
- Washington State Department of Ecology. 2007. Workbook Tools for Calculating Soil and Groundwater Cleanup Levels Under the Model Toxics Control Act Cleanup Regulation. User's Guide for MTCATPH 11.1 & MTCASGL 11.0. Publication No. 01-09-073. December.

The processes that will be followed in the HHRA, and the methodologies and assumptions that will be applied, are described below.

Comparison to Drinking Water Criteria

Estimated water concentrations of COIs at points of potential contact with exposure populations will be compared to U.S. Federal or State drinking water quality criteria, if available, including the following:

- U.S. EPA Safe Drinking Water Act (SDWA) National Primary Drinking Water Regulations Maximum Contaminant Levels (MCLs) or Washington State Department of Health MCLs for drinking water
- U.S. EPA Drinking Water Health Advisories (HAs), in units of µg/L
- Washington State Water Quality Standards for Ground Waters– Chapter 173-200 WAC

- Washington State Model Toxics Control Act (MTCA) Groundwater Cleanup Standards (Chapter 173-340 WAC, Method B and C)

Results will be tabulated for each scenario and location of interest and presented in the HHRA report.

Quantification of Potential Human Health Risks

Potential human health risks associated with exposure to COIs for each of the scenarios of interest will be evaluated using standard U.S. EPA human health risk assessment methodologies. The approach is described below.

1. Identify Subset of COIs for HHRA Following Fate and Transport Modeling

At the completion of fate and transport modeling, HDR will compare estimated "worst-case" concentrations of the chemicals of interest (COIs) at potential points of exposure to drinking water equivalent levels (DWELs) generated by Intertox in the Screening Level Evaluation. It is assumed that these will be concentrations of COIs estimated at groundwater wells, in any aquifer. Intertox will review these results and identify a subset of chemicals that warrant further evaluation in the HHRA (i.e., those chemicals with worst-case exposure point concentrations predicted to exceed DWELs).

It is assumed that the COIs evaluated by HDR will consist of those identified in the Screening Level Evaluation as warranting further evaluation (Table 1).

Table 1. Chemicals Recommended for Inclusion in the HHRA Based on the Results of the Screening Level Evaluation

Chemical	CAS Number	Category or Pharmaceutical Class	Reason for Inclusion
Hormones			
Androstenedione	63-05-8	Steroid hormone	Hormone
Estradiol	50-28-2	Estrogenic hormone	Exceeds DWEL
Estradiol – 17 beta	50-28-2	Estrogenic hormone	Hormone
Estriol	50-27-1	Hormone	Hormone
Estrone	53-16-7	Estrogenic hormone	Exceeds DWEL
Ethinyl Estradiol - 17 alpha	57-63-6	Contraceptive hormone	Exceeds DWEL
Norethisterone	68-22-4	Steroid hormone	Exceeds DWEL
Progesterone	57-83-0	Steroid hormone	Hormone
Testosterone	58-22-0	Steroid hormone	Hormone and ≥ 10% DWEL but < DWEL
PPCPs and Other Personal Products			
Acesulfame-K	55589-62-3	Sugar substitute	≥ 10% DWEL but < DWEL
Albuterol	18559-94-9	Anti-asthmatic	Exceeds DWEL
Atenolol	29122-68-7	Beta blocker	≥ 10% DWEL but < DWEL
Carbamazepine	298-46-4	Antiseizure	Exceeds DWEL
Chloramphenicol	56-75-7	Antibiotic	Exceeds DWEL
Cotinine	486-56-6	Nicotine degradate	≥ 10% DWEL but < DWEL
Diazepam	439-14-5	Antianxiety	≥ 10% DWEL but < DWEL
Diclofenac	15307-86-5	Anti-inflammatory	≥ 10% DWEL but < DWEL

Chemical	CAS Number	Category or Pharmaceutical Class	Reason for Inclusion
Dilantin	57-41-0	Antisiezure	≥ 10% DWEL but < DWEL
Fluoxetine	54910-89-3	Antidepressant	≥ 10% DWEL but < DWEL
Gemfibrozil	25812-30-0	Antilipidemic	≥ 10% DWEL but < DWEL
Lopressor	51384-51-1	Beta Blocker	≥ 10% DWEL but < DWEL
Primidone	125-33-7	Anti-convulsant	Exceeds DWEL
Sucralose	56038-13-2	Sugar substitute	≥ 10% DWEL but < DWEL
Sulfamethoxazole	723-46-6	Sulfa antibiotic	≥ 10% DWEL but < DWEL
Theophylline	58-55-9	Anti-asthmatic	≥ 10% DWEL but < DWEL
Industrial chemicals and Pesticides			
1,4-Dioxane	123-91-1	Industrial chemical	Exceeds DWEL
4-Nonylphenol	104-40-5	Surfactant	Exceeds DWEL
N-Nitroso dimethylamine (NDMA)	62-75-9	Industrial solvent	Exceeds DWEL
Quinoline	91-22-5	Industrial chemical	Exceeds DWEL
Thiabendazole	148-79-8	Fungicide	≥ 10% DWEL but < DWEL
Tris(2-carboxyethyl)phosphine (TCEP)	115-96-8	Flame retardant	≥ 10% DWEL but < DWEL
Tris(1,3-dichloroisopropyl)phosphate (TDCPP)	13674-87-8	Flame retardant	Exceeds DWEL
Perfluorochemicals			
Perfluoro butanoic acid (PFBA)	375-22-4	Perfluorochemical	PFAS
Perfluoro octanesulfonate (PFOS)	45298-90-6	Perfluorochemical	PFAS
Perfluoro octanesulfonic acid	1763-23-1	Perfluorochemical	PFAS
Perfluoro octanoic acid (PFOA)	15899-31-7	Perfluorochemical	PFAS and ≥ 10% DWEL but < DWEL
Perfluoro-1-butanesulfonate	194999-85-4	Perfluorochemical	PFAS
Perfluoro-1-butanesulfonic acid	375-73-5	Perfluorochemical	PFAS
Perfluoro-1-hexanesulfonate	108427-53-8	Perfluorochemical	PFAS
Perfluoro-1-hexanesulfonic acid	355-46-4	Perfluorochemical	PFAS
Perfluoro-n-decanoic acid	335-76-2	Perfluorochemical	PFAS
Perfluoro-n-heptanoic acid	375-85-9	Perfluorochemical	PFAS
Perfluoro-n-hexanoic acid	307-24-4	Perfluorochemical	Exceeds DWEL
Perfluoro-n-nonanoic acid	375-95-1	Perfluorochemical	≥ 10% DWEL but < DWEL
Perfluoropentanoic acid	2706-90-3	Perfluorochemical	Exceeds DWEL

DWEL – Drinking Water Equivalent Level (established in Screening Level Evaluation); PFAS – polyfluoroalkyl substances; PPCP – pharmaceutical and personal care product ingredients

No deliverable for this subtask is assumed. It is assumed that Intertox will engage in Email correspondence and phone discussions with HDR, and that HDR and Intertox will communicate results at a Science Task Force meeting.

2. Conduct Exposure Assessment

Using the subset of COIs identified in the previous step, Intertox will proceed with the Exposure Assessment.

The goals of this step are to identify and characterize populations that could be exposed to residual chemicals in reclaimed water and the pathways through which they could be exposed, and to develop chemical-specific estimates of average daily dose. For each population, chemical, and

pathway, exposure will be quantified using U.S. EPA recommended methodologies and equations (i.e., in a manner consistent with the guidance documents listed above).

Steps in the Exposure Assessment will include:

a) Characterize exposure scenarios/activities

For each of the reclaimed water treatment scenarios to be considered in this Study, Intertox will evaluate potential exposures to the subset of residual chemicals that were identified following the fate and transport modeling as warranting further consideration. The primary exposure scenario that will be considered for each of the treatment/groundwater recharge scenarios is exposure to potable water from domestic or municipal water supply wells (e.g., exposure to adult and child residents, via dermal contact and incidental ingestion).

Where the results of fate and transport modeling suggest the potential for transport of significant concentrations of residual chemicals (i.e., at concentrations that exceed DWELs) to other points of potential contact with members of the public, we will also consider the following activities and exposure scenarios:

- Irrigation at parks (e.g., exposure to adult park/maintenance workers and children at play fields, via dermal contact and incidental ingestion)
- Irrigation at golf courses (e.g., exposure to adult maintenance workers and golfers, via dermal contact and incidental ingestion)
- Exposure to a recreational water feature (e.g., exposure to children, via dermal contact and incidental ingestion)
- Exposure to surface water (i.e., streams) recharged by groundwater (e.g., exposure to adults and children, via dermal contact during wading, incidental ingestion and dermal contact during swimming).
- Exposure through ingestion of fish that take up contaminants from surface water (e.g., exposure to adults and children).

Final designation of exposure scenarios and activities to be considered will be determined after examination of fate and transport modeling results and consultation with advisory committee members.

b) Identify potential exposure locations based on results of fate and transport modeling

Potential exposure locations to residual chemicals in water from domestic/municipal water supply wells, groundwater, and surface water will be identified based on the results of the fate and transport modeling. It is assumed that this information will be provided to Intertox by HDR.

c) Identify exposure populations

Exposure populations that will be evaluated may include the following, depending on the exposure medium and exposure location:

- child resident
- adult resident

- adult worker

In order to ensure protection of other sensitive subgroups (e.g., pregnant women, immunodeficient populations, the elderly), the risk assessment will use toxicity criteria that incorporate safety factors intended to be protective of potential exposures to these populations, per U.S. EPA guidelines. In addition, more detailed characterization of exposure to particular subpopulations (e.g., pregnant woman/ fetus, infants or young children) may be considered on a chemical-specific basis if warranted upon examination of the toxicological data.

d) Identify exposure pathways

Potential routes of exposure that will be assessed for the above scenarios and exposure populations include:

- ingestion of domestic potable water
- incidental ingestion of groundwater
- incidental ingestion of surface water (e.g., in streams)
- dermal contact with domestic potable water
- dermal contact with groundwater
- dermal contact with surface water

The potential for inhalation of chemicals in aerosols or vapors will be considered. However, it is expected that the contribution of the inhalation pathway will be insignificant compared to other exposure pathways for the relatively nonvolatile chemicals that could reach domestic/municipal supply wells or surface water. In addition, the potential for exposure to residual chemicals through uptake into and consumption of fish will be considered if fate and transport modeling predicts transport of residual chemicals to surface water systems.

For a given chemical, estimated exposures/risks for all pathways relevant to a hypothetical exposed individual under a given exposure scenario will be assumed to be additive.

The general equations that will be used to estimate intake (dose) for each pathway identified as potentially complete are provided below.

Ingestion of Domestic/Municipal, Ground, or Surface Water

$$Dose_{ing-water}\ (mg/kg-d) = \frac{C_{water} \times IR_{water} \times ET \times EF \times ED}{BW \times AT}$$

Where:

Dose	=	Average daily dose (ADD) for noncarcinogens or Lifetime Average Daily Dose (LADD) for carcinogens, from ingestion of domestic, ground, or surface water, mg/kg-d
C_{water}	=	Concentration of contaminant in domestic, ground, or surface water based on fate and transport modeling, mg/L
IR_{water}	=	Domestic, ground, or surface water ingestion rate, L/hr
ET	=	Exposure time, hr/event

EF = Exposure frequency, event/yr
ED = Exposure duration, yr
BW = Body weight, kg
AT = Averaging time, d (equal to exposure duration for noncarcinogens and 70 years for carcinogens)

Dermal Contact with Domestic/Municipal, Ground, or Surface Water

$$Dose_{derm-water}\ (mg/kg-d) = \frac{C_{water} \times SA \times K_p \times CF \times ET \times EF \times ED}{BW \times AT}$$

Where:

Dose = Average daily dose (ADD) for noncarcinogens or Lifetime Average Daily Dose (LADD) for carcinogens, from dermal contact with domestic, ground, or surface water, mg/kg-d
C_{water} = Concentration of contaminant in domestic/municipal, ground, or surface water based on fate and transport modeling, mg/L
SA = Skin surface area available for contact with water, cm^2
K_p = Chemical-specific dermal permeability constant, cm/hr
CF = Conversion factor, L/cm^3
ET = Exposure time, hr/event
EF = Exposure frequency, event/yr
ED = Exposure duration, yr
BW = Body weight, kg
AT = Averaging time, d (equal to exposure duration for noncarcinogens and 70 years for carcinogens)

Consumption of Fish

$$Dose_{fish}\ (mg/kg-d) = \frac{C_{fish} \times IR_{fish} \times f_i \times EF \times ED \times CF}{BW \times AT}$$

Where:

Dose = Average daily dose (ADD) for noncarcinogens or Lifetime Average Daily Dose (LADD) for carcinogens, from fish consumption, mg/kg-d
C_{fish} = Concentration of contaminant in edible portion of fish, mg/kg (see below)
IR_{fish} = Fish ingestion rate, g/d
f_i = Fraction ingested from a contaminated source, unitless
EF = Exposure frequency, d/yr
ED = Exposure duration, yr
CF = Conversion factor, kg/g
BW = Body weight, kg
AT = Averaging time, d (equal to exposure duration for noncarcinogens and 70 years for carcinogens)

If appropriate, chemical-specific bioaccumulation factors (BAFs), where available, will be used to estimate fish tissue concentrations from surface water concentrations, as follows:

$$C_{fish}\ \left(\frac{mg}{kg}\right)\ = C_{water}\ \times\ BAF$$

Where:

C_{fish}	=	Concentration of contaminant in edible portion of fish, mg/kg
C_{water}	=	Concentration of contaminant in surface water based on fate and transport modeling, mg/L
BAF	=	Chemical-specific bioaccumulation factor into fish, L/kg

Final designation of potential exposure pathways will be determined after evaluation of project sampling and fate and transport (Task 2) data, and consultation with the advisory committees.

e) Estimate exposure point concentrations (EPCs)

Once potentially exposed populations and exposure media and pathways are identified, estimated environmental concentrations at points of potential exposure will be identified. It is assumed that these estimates will be generated by HDR as part of the groundwater fate and transport modelling and will be provided to Intertox for purposes of conducting the HHRA, and may include concentrations in potable water from domestic and municipal water supply wells, groundwater concentrations, and surface water concentrations.

f) Identify population- and scenario-specific exposure estimates

For each of the populations and scenarios identified above, two levels of exposure will be evaluated to provide perspective on a range of possible exposures and risks for the populations of interest:

- an upperbound exposure (i.e., reasonable maximum exposure (RME))— this will be defined as the highest exposure that could reasonably be expected to occur for a given exposure pathway at a site, and will account for both uncertainty in the contaminant concentration and variability in the exposure parameters
- a more likely exposed (MLE) or central estimate exposure— this will provide an estimate of more "average" levels of exposure

Population- and scenario-specific exposure estimates will be used to quantify potential exposures. Where available, site-specific information on exposure rates and exposure frequency and duration will be applied (e.g., information on recreational activities or irrigation patterns). In the absence of site-specific information, information on average exposures to U.S. populations, as presented for example in U.S. EPA's *Exposure Factors Handbook* (U.S. EPA, 2011a; 2019a) or U.S. EPA standard default exposure parameters (e.g., U.S. EPA, 1991) will be used.

Factors that will be considered in selecting exposure parameter values for specific activities are discussed below.

- *Recreational activity patterns*. As available and appropriate, recreational activity patterns (e.g., frequency of participation in recreational activities in potential impacted creeks, such as

wading, swimming, or boating) will be based on information collected at or near the study area. In the absence of such information, information gathered by U.S. EPA and other agencies and professional judgment will be used to establish these parameters, in order to present a range of potential risks.

- *Fish consumption rates*. Fish consumption values for angler populations evaluated in the HHRA will assume that the populations of interest are recreational anglers who fish regularly for recreation or sport and their family members who consume the recreationally caught fish, as well as subsistence anglers (i.e., members of the Squaxin Island Tribe), if subsistence angler-specific fish consumption rates are available. Since site-specific information on fish consumption rates have not been collected as part of this project, data from other regional studies will be used to assess exposures via this pathway.
- *Chemical-specific uptake factors.* Chemical-specific uptake factors will be identified from U.S. EPA guidance documents and the scientific literature, as appropriate. These uptake factors will include:
  - Permeability constants (K_p)—to estimate the rate at which a chemical is partitioned between skin and water
  - Gastrointestinal absorption factors (GAF)—to estimate the rate at which a chemical or compound is absorbed from the gastrointestinal tract of a human, for use in adjusting administered dose oral RfDs or slope factors to absorbed dose dermal RfDs or slope factors
  - Bioaccumulation factors (BAF)—to estimate the rate at which a chemical is accumulated from surface water into fish tissue

g) Derive dose estimates

For each exposure scenario, chemical-specific dose estimates will be derived for each exposure pathway. Doses will be presented in units of milligrams per kilogram body weight per day (mg/kg-d). For evaluation of noncarcinogenic effects, doses will be averaged over one year and presented as average daily doses (ADDs). For evaluation of cancer risk, doses will be averaged over a lifetime (assumed to be 70 years) and presented as lifetime average daily doses (LADDs). These dose estimates will then be compared to toxicity information as part of the Risk Characterization.

3. Conduct Toxicity Assessment

In this step, toxicity reference values will be identified for the residual chemicals included in the HHRA. These values will be used to evaluate the likelihood of adverse health effects from estimated exposures. Values considered will include noncancer or cancer-based toxicity reference values in units of mg/kg-d to be compared to estimated average daily doses (calculated per the methodologies described in 2. Characterize Potential Exposures, above). Types and sources of values that will be considered are described below.

<u>Toxicity reference values for noncancer and cancer effects</u>

Average daily doses to populations of interest (as calculated per the methodologies described in 2. Characterize Potential Exposures, above) will be evaluated to assess the potential for noncancer and cancer health effects by comparing them to toxicity reference values for noncancer and cancer endpoints, as follows:

- To evaluate the potential for noncarcinogenic effects, exposures will be evaluated using the Hazard Index (HI) approach (U.S. EPA, 1989). For each exposure scenario, chemical- and pathway-specific Hazard Quotients (HQs) will be calculated by dividing the estimated ADD by a chemical-specific noncancer acceptable daily intake (ADI), as follows:

$$HQ = \frac{ADD\ (mg/kg-d)}{Noncancer\ ADI\ (mg/kg-d)}$$

  HQs will then be summed for all exposure pathways for the chemical that are assumed to be complete under that scenario, to derive a HI for that chemical.
- To evaluate cancer risks, pathway-specific excess cancer risks for exposure to the carcinogenic chemicals of interest under a given exposure scenario will be calculated by multiplying the LADD estimate by a chemical-specific cancer slope factor (SF), as follows:

$$Excess\ Cancer\ Risk = LADD\ (mg/kg-d) \times SF\ (mg/kg-d)^{-1}$$

The main sources of toxicity reference values applicable to human health risk assessments include values derived by U.S. EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and U.S. state environmental or human health departments. These criteria will be used in the HHRA as available, to calculate noncancer hazard and cancer risk. For many of the residual chemicals identified as chemicals of interest for the HHRA, toxicity criteria for long-term low-level environmental exposure are not available, as discussed in the Screening Evaluation. For these chemicals, toxicity reference values will be derived using standard and accepted risk assessment methodologies, as described below. The types of published toxicity reference values that will be considered and the methodologies for deriving values for those chemicals lacking published values are summarized below.

Sources of published toxicity reference values for noncancer and cancer effects

For each chemical of interest evaluated in the HHRA, the availability of published toxicity reference values for noncancer and cancer effects will be determined by conducting a search of the regulatory and toxicological literature. In general, in the event that multiple published toxicity values are available, well-documented peer-reviewed U.S. federal or state values will be given priority. Recency of values and the extent to which the published values consider new or recently developed toxicological data will also be considered. For each chemical of interest, the rationale for the selection of particular values, and the basis of those values, will be documented.

Sources of U.S. Federal or State government health risk-based toxicity criteria that will be considered include:

- U.S. EPA Integrated Risk Information System (IRIS) Cancer Slope Factors (SFs) or noncancer Reference Doses (RfDs) for chronic exposures, in units of $(mg/kg\text{-}d)^{-1}$ or mg/kg-d, respectively.
- U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) for noncancer effects, for subchronic and chronic exposures, in units of mg/kg-d.

- ATSDR Minimal Risk Levels (MRLs) for noncancer effects, for intermediate and chronic duration exposures, in units of mg/kg-d.
- California EPA oral SFs for cancer, in units of $(mg/kg\text{-}d)^{-1}$.
- California EPA Public Health Goals (PHGs) for drinking water, in units of µg/L.
- California EPA No Significant Risk Levels (NSRLs) for cancer and reproductive/ developmental toxicity developed as part of the Proposition 65 program, in units of µg/d.
- Minnesota Department of Health (MDH) Human Health-Based Values (HBVs) or noncancer Human Risk Limits (nHRLs) for drinking water, in units of µg/L.

Other types of acceptable daily intakes (ADIs) developed by authoritative bodies will also be considered in the absence of published peer reviewed values as listed above, including values from the European Food Safety Authority (EFSA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). The selection of such values will be based on the availability and validity of information documenting their basis.

In the event that noncancer health risk-based toxicity reference values for drinking water are given in units other than mg/kg body weight-d (e.g., in units of µg/L or µg/d) they will be converted to daily doses using appropriate average drinking water ingestion rates and/or body weights.

For chemicals of interest without published peer-reviewed ADIs of acceptable quality, ADIs will be derived using a modification of the approach applied in the Screening Evaluation, as described below.

Derivation of noncancer ADIs from NOAELs or LOAELs identified in toxicological studies

For compounds without acceptable published peer-reviewed ADIs, ADIs for noncancer endpoints will be derived from no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELs) for noncancer effects reported in animal toxicity studies or studies in humans (e.g., clinical trials), if available. ADIs derived using this approach are assumed to correspond to the amount of a chemical to which a person, including members of sensitive subpopulations, can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect (U.S. EPA, 1993).

When establishing guidelines or standards for noncarcinogenic effects, including RfDs (U.S. EPA, 2002), MRLs (ATSDR, 2007), and tolerable daily intakes (TDIs) (WHO, 1994), agencies charged with developing guidance values typically identify some threshold level of exposure below which adverse health effects have not been observed and, based on review of toxicity data, identify a corresponding point of departure upon which to base the guidance level. This is typically the highest dose at which an effect is not seen (the NOAEL) or the lowest dose at which an effect is seen (the LOAEL). Below this dose, there is no evidence in animals or humans of a statistically or biologically significant increase in adverse effects, although some changes may occur that are not considered adverse (e.g., changes in certain enzyme levels). This "point of departure" is then divided by uncertainty factors (UFs) to derive a value considered protective to broader population groups, including sensitive populations such as children or people with immune compromised systems, e.g.:

$$ADI_{toxicity\ data-based}\ (mg/kg-d) = \frac{NOAEL\ or\ LOAEL\ (mg/kg-d)}{UFs}$$

Study types of most relevance for evaluating long-term low-level exposures to compounds in water are subchronic, chronic, reproduction, and developmental toxicity (teratology) studies with exposure primarily via the oral route. The studies primarily assessed impacts on mice and rats, but could also include rabbits, dogs, primates, and other animals.

Generally, several multiplicative UFs are applied, individually ranging in value from 3 to 10 with each factor representing a specific area of uncertainty in the available data (e.g., intraspecies uncertainty/ variability, interspecies uncertainty/ variability, extrapolation from a LOAEL to a NOAEL, extrapolation from less-than-lifetime exposure to lifetime exposure, and database uncertainties). When high quality toxicity data are available, combined uncertainty factors typically range from 30 to 1,000. Per U.S. EPA risk assessment guidance (U.S. EPA, 2008), a factor of 3 represents a "partial" uncertainty factor, equal to the half-log (square root) of 10 (i.e., $10^{1/2}$), usually rounded to 3 for use in risk assessment. As such, by convention, when two UFs with a value of 3 are multiplied together, the resulting combined UF is 10 (not 3 × 3 =9). For compounds evaluated in the HHRA that do not have existing toxicity criteria, chemical-specific UFs will be identified and applied based on the selected critical study as well as the quality of the toxicological database for the compound.

To calculate an ADI from animal toxicity data, identified point of departures (e.g., NOAELs or LOAELs from toxicity studies) will be converted to human equivalent doses (HEDs) based on body weight scaling. Per U.S. EPA (2011b) recommendations, body weight (BW) scaling to the ¾ power ($BW^{3/4}$) will be used in combination with a reduced default interspecies uncertainty factor of 3 (rather than the full default value of 10 applied in the absence of body weight scaling) to calculate the ADI.

Selection of an appropriate critical study for the derivation of toxicity criteria will take into account U.S. EPA's guidance for evaluating the acceptability of open literature studies (U.S. EPA, 2012), including consideration of the nature of the test substance, the test organism, number of organisms tested per dose and number of dose levels evaluated, husbandry conditions, exposure method, route, and frequency of administration, length of treatment period, controls, macro- and microscopic observations of test animals, statistical methods applied, etc. In general, the study of appropriate quality that yields the lowest ADI using the above methods will be selected for use in the HHRA.

Derivation of ADIs based on the lowest therapeutic dose of pharmaceuticals

The lower end of a drug's therapeutic range can be considered an estimate of the threshold for appreciable biological activity in target populations, and therefore may be considered a threshold for potential adverse effects. In the absence of sufficient or appropriate data from toxicological studies, following an approach analogous to the NOAEL/ LOAEL approach, ADIs for pharmaceutical compounds may be derived by dividing the lowest therapeutic dose by UFs to account for extrapolation from the LOAEL to a NOAEL, variations in susceptibility between different members of the population, or data gaps:

$$ADI_{therapeutic\ dose-based}\ (\mu g/kg-d) = \frac{Lowest\ Therapeutic\ Dose\ (\mu g/kg-d)}{UFs}$$

As above, for compounds evaluated in the HHRA that do not have existing toxicity criteria or sufficient toxicological data to derive an ADI, chemical-specific UFs will be identified and applied based on the identified therapeutic dose as well as the quality of the toxicological database for the compound. When applying this approach, the lowest therapeutic dose will be considered to be analogous to a LOAEL.

Derivation of cancer slope factors for carcinogenicity based on tumor incidence data

For chemicals with evidence of genotoxicity and evidence of carcinogenicity in high dose animal studies, a linear extrapolation model will be used to predict the tumorigenic response at low doses if sufficient data on tumor incidence per dose level are available. These types of models assume a linear relationship between risk and dose at low doses (i.e., they assume the absence of a threshold below which there is no risk; U.S. EPA, 2005). These models are conservative (health-protective) and are applied when there is an absence of sufficient information on modes of action or when the mode of action information indicates the dose-response curve at low dose is expected to be linear. The slope of the risk/dose line, known as the slope factor (SF), is an upper-bound estimate of risk per increment of dose (e.g., per 1 mg/kg-d of exposure) that can be used to estimate risk probabilities for different exposure levels.

If sufficient data on tumor incidence per dose level are available for a given compound with evidence of carcinogenicity in animal bioassays, and data indicate that the compound is genotoxic and assumed to have a linear relationship between carcinogenicity and dose, a multi-stage carcinogenicity model will be used to estimate a SF. For these compounds, U.S. EPA's Benchmark Dose Software v.3.1.2 (BMDS 3.1.2) (U.S. EPA, 2019b) will be used to model the data in the observed range and estimate a benchmark dose level (BMDL) for a benchmark response of 10% extra risk, which is generally at the low end of the observable range for standard cancer bioassay data. This BMDL serves as the "point of departure" for linear extrapolation.

In the Screening Level Evaluation, some of the evaluated chemicals reportedly showed evidence of carcinogenicity in animal studies, but tumor incidence data were not located and so a cancer SF could not be derived. In these cases, an alternative approach to estimating cancer risk was applied. Specifically, if genotoxicity data indicated the compound is a nongenotoxic carcinogen but no tumor incidence data were identified, an additional UF of 10 was applied to the lowest therapeutic dose or the NOAEL/ LOAEL to develop an ADI. If genotoxicity data indicated the compound is a genotoxic carcinogen but no tumor incidence data were identified, an ADI was derived by dividing the maximum tolerated dose by 740,000 (per the Gaylor and Gold (1998) Virtually Safe Dose (VSD) approach for genotoxic carcinogens). Application of these approaches will be considered in the HHRA if necessary for the selected chemicals of interest.

Derivation of ADIs for antibiotics based on Minimum Inhibitory Concentrations

If appropriate, ADIs for antibiotics will be developed based on the minimum inhibitory concentration (MIC) to human gastrointestinal flora, defined as the lowest concentration of the antibiotic that will inhibit the visible growth of the microorganism (WHO, 1997; EMEA, 1998; Schwab et al., 2005; WHO, 2006). ADIs will be developed from MICs using the following equation (WHO, 1997; 2006):

$$ADIs_{MIC}\ (\mu g/kg-d) = \frac{MIC_{50}\ (mg/g) \times MCC\ (g/d) \times 1{,}000\ \mu g/mg}{FA\ \times SaF\ \times BW\ (kg)}$$

Where:

MIC_{50}	=	Minimum inhibitory concentration of 50% of strains of the most sensitive relevant organism (mg/g, equivalent to µg/mL) [WHO (1997, 2006) is clear that the MIC_{50}, as opposed to the MIC, should be applied in the calculation]
MCC	=	Mass of colonic contents (g/day)
FA	=	Fraction of the dose available to the gastrointestinal microflora
SaF	=	Safety factor, with a magnitude depending on the quality and quantity of the microbiological data available
BW	=	Body weight (kg)

To develop an ADI per this approach, the MIC for the most sensitive bacterial strain determined in susceptibility assays will be selected (KnowledgeBase, 2019). Fraction available (FA) will be determined from the results of human clinical studies, or assumed to be 50% when no data were available. The mass of colonic contents (MCC) will be assumed to be 220 g/day, as estimated by WHO (1997), and the assumed body weight (BW) of 80 kg will be selected based on U.S. EPA's default body weight for adults. A safety factor (SaF) of 10 will be applied to account for limitations in the database.

4. Conduct Risk Characterization

In this step, Intertox will combine the results of the previous three steps to develop estimates of noncancer hazards and cancer risks for each chemical for each of the exposure scenarios considered in accordance with U.S. EPA guidance on characterizing risks (e.g., U.S. EPA, 1989; 2014; 2018a).

For each scenario and receptor, estimated noncancer hazards and cancer risks will be compared to health-based benchmarks or comparison points for noncancer hazard or cancer risk on a chemical-by-chemical basis.

Noncancer hazards will be compared to an acceptable hazard level of 1 or unity (i.e., an exposure level equal to the ADI). Cancer risks will be compared to range of acceptable cancer risk levels. For example, risk levels ranging from one in 10,000 (1E-04) to one in a million (1E-6, the accepted *de minimis* cancer risk level) have been considered acceptable by U.S. EPA under various programs and at various sites (U.S. EPA, 2018b; U.S. EPA, 2000).

5. Evaluate the Potential Significance of Findings for "Indicator Compounds"

In this step, findings from the health risk evaluation will be extrapolated as possible to other compounds that are either structurally or mechanistically similar to assess the effectiveness of different treatment processes at reducing overall health risks.

6. Characterize the Uncertainty in Risk Estimates

In this step, Intertox will conduct a qualitative analysis to describe the components of the health risk evaluation that are likely to contribute most significantly to uncertainties in the overall risk estimates, and the likely effect of these factors on risk estimates (e.g., over- or under-estimation).

7. Summarize Relative Risk Results and Develop Information to Support Risk Communication

In this step, Intertox will summarize the results of the HHRA. In addition to presenting quantitative risk estimates, this information will provide perspective on the relative significance of the exposures and risks compared to risk benchmarks and other sources of exposure, to support risk communication efforts. In particular, Intertox will:

- Summarize comparisons of estimated exposure point concentrations to published federal or state drinking water criteria, where available.
- Present chemical-specific estimates of noncancer hazards and excess cancer risks for each of the scenarios and populations.
- Describe how the estimated noncancer hazards and cancer risks compare across exposure scenarios, and identify the scenarios and populations likely to have the most significant risks.
- Identify which of the residual chemicals and which pathways contribute most significantly to risks.
- Describe how the estimated risks compare to *de minimis* risk levels or comparison points established by various authoritative bodies for different exposure scenarios (e.g., U.S. EPA, the Washington Department of Ecology).
- Describe margins of exposure between a point of departure for an adverse effect (e.g., a toxicity reference value or the toxicological endpoint that is the basis for that value) and measured or estimated environmental levels.
- Identify the factors likely to contribute most significantly to uncertainties in risk estimates.
- Discuss significance of the findings for the chemicals of interest evaluated in the HHRA for other similar compounds not included in the assessment (e.g., compounds in the same structural or product use classes).
- Present risk metrics to put magnitudes of estimated risks into perspective (e.g., how many glasses of water one would have to drink with the measured concentrations to exceed the risk guidelines).
- Compare potential exposures to residual chemicals in media potentially impacted by reclaimed water to other sources of exposure through unrelated pathways (e.g., in food, beverages, medications).

8. HHRA Technical Report

Intertox will prepare a Technical Report that summarizes the results of the HHRA and in particular the information described in Subtask 3.2.2.7.

Deliverables

1) Technical Report #2 (HHRA). Draft, Revised Draft, and Final versions.
2) Presentations and handouts for meetings with the Task Force and Peer Review.

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