Update for ATSDR Health Assessors

Including APPLETREE Partners
(Internal Use Only)

DCHI Guidance & Clearance News

April 2020

The purpose of this newsletter is to keep you informed about the guidance and resources that are available for use in your health evaluations.

Managing the "Grey Zone" can be complicated (Part 2).

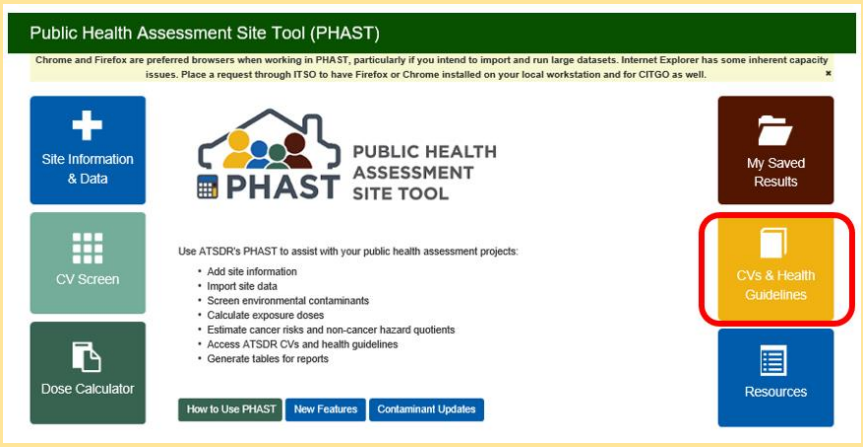
In the January 2020 ADS Newsletter, the ADS Group provided some tips on how to calculate a margin-of-exposure (MOE) and how to use this metric to help determine if harmful effects are possible. Below we discuss other aspects of managing the "Grey Zone" from using the hazard quotient (HQ) to an overview of the steps for conducting a toxicological evaluation to determine if harmful non-cancer effects are possible.

- **Using an HQ**: the HQ is good for determining whether an exposure needs to be further evaluated by using other information like the MOE. Moreover, it is only a measure of how many times the exposure dose is above the health guideline for a given pathway and chemical. Although it does provide some measure of increasing risk, in the final analysis, it cannot tell you if harmful effects are possible. The interpretation of the MOE is a better metric to use to help determine if you are in the range where harmful non-cancer effects are possible. However, the evaluation of the MOE is not the only information needed to make a final determination.

- **Quick Overview for Determining Non-cancerous Effects** (see Conducting an In-Depth Toxicological Evaluation—Case Study in SharePoint under the *NCEH/ATSDR Partners>Division of Community Health Investigations>Health Assessment Guidance>Guidance Documents* section for more details
  - Step 1: Review Levels of Significance (LSE) figure and tables in the toxicological profile
  - Step 2: Identify studies and endpoints used to develop the MRL or RfD
  - Step 3: Identify other studies and endpoints with similar doses
  - Step 4: Review the following:
    - MRL worksheet or Health Information in the PHAST Database (see below for more information) to understand the MRL basis (review IRIS for RfD)
    - Other endpoints that are relevant
    - Journal articles, if necessary
  - Step 5: Decide which health effects might be possible (see slides 14 and 16-19 on Mellard presentation). You should consult with an ADS or toxicologist to help you evaluate the "grey zone" as it takes experience and expertise to determine whether an exposure dose is harmful or not.
  - Step 6: Include discussion about uncertainty

Please contact the ADS Group if you need more guidance on how to manage the "grey zone" for your site!

Finding Important Health Information in the PHAST Database



The CVs & Health Guidelines module in PHAST contains important information about health effects. The information will help you determine the harmful effects that might be possible when site-specific doses exceed health guidelines, such as MRLs, RfDs, and RfCs. To find this information, go to PHAST's CVs & HG tab, enter the chemical, and select "View Contaminant Information"

Important information about the chemical will appear in the contaminant notes section followed by tables showing the information about MRLs, RfD, RfCs, and cancer.

BENZENE

CASRN: 000071-43-2 **Date Last Updated:** 4/8/2020

Health Guidelines | Drinking Water CVs | Soil CVs | Air CVs | SVI CVs | Contaminant Info

Contaminant Notes

Health assessors should use ATSDR's chronic oral and inhalation MRLs to decide the risk of non-cancerous harmful effects because the MRLs are significantly lower than the RfD and RfC.

Oral slope factor ranges from 0.015 - 0.055 $(mg/kg/day)^{-1}$.

Non-Cancer Health Guidelines

Oral (mg/kg/day)

Chronic		Intermediate	Acute
ATSDR MRL	EPA RfD	ATSDR MRL	ATSDR MRL
0.0005	0.004		

Inhalation (µg/m³)

Chronic		Intermediate	Acute
ATSDR MRL	EPA RfC	ATSDR MRL	ATSDR MRL
9.6	30	19	29

Inhalation (ppb)

Chronic		Intermediate	Acute
ATSDR MRL	EPA RfC	ATSDR MRL	ATSDR MRL
3.0	9.4	6.0	9.0

Quantitative Estimates of Carcinogenic Risk

Oral Slope Factor	
CSF	0.055 $(mg/kg/day)^{-1}$
Source	EPA

Inhalation Unit Risk	
IUR	7.8E-06 $(\mu g/m^3)^{-1}$
Source	EPA

Cancer Classifications

Agency	Cancer Class*	Description	Year
EPA	KL	Known/Likely human carcinogen	2000
NTP	1	Known human carcinogen	2016
IARC	1	Carcinogenic to humans (sufficient human evidence)	2018
NIOSH	OC	Occupational carcinogen	

*Some cancer class abbreviations were created by ATSDR and are listed here for ease of use only, and do not represent official agency classification.

Is contaminant classified as a mutagen? No
Are ADAFs applied in PHAST? No

If you scroll down to the oral or inhalation "Health Guideline Information," you will find a table summarizing the basis for each health guideline. When an MRL or RfD/RfC is developed from multiple studies, each study will be summarized by showing the species, target system, study effect, uncertainty factor, and study health effects.

The study health effects is where the most important information is described. This text summarizes the information in the MRL worksheet or IRIS profile and highlights the final toxicity value (e.g., LOAEL, $LOAEL_{ADJ}$, BMDL, BMCL, HED, HEC) that should be used. Health assessors should compare site-specific doses and concentrations to this final toxicity value when deciding harmful effects. For example, to evaluate benzene exposure, health assessors should compare site-specific doses to the $BMDL_{0.25sd,ADJ}$ of 0.014 mg/kg/day. The description of the study health effects explains that the oral $BMDL_{0.25sd,ADJ}$ was derived from an inhalation LOAEL using benchmark dose modeling. If site-specific doses approach or exceed the oral $BMDL_{0.25sd,ADJ}$ of 0.014 mg/kg/day, it's reasonable to assume that people could be at risk of reduced white blood cells and platelet counts. When appropriate, the health effects text will mention other sensitive systems or organs that should be evaluated.

Because science often supports benchmark dose modeling or conversion to human equivalent doses/concentrations, toxicity values like BMDL, BMCL, HED, and HEC are becoming more common. These values are often significantly lower than the original LOAEL reported in the LSE table in the tox profile. When these values are available, health assessors should use them over study LOAELs and NOAELs when deciding the risk of harmful effects. If an abbreviation used above is not familiar, refer to the "PHAST Acronyms & Abbreviations" document in the PHAST resource page.

Oral Health Guideline Information

Species	Target System	Study Effect		Uncertainty Factor (Total)	Study Health Effects	Citation(s)
		Type	Level			
ATSDR Chronic MRL: 0.0005 mg/kg/day						
Human	hematological	$BMDL_{0.25sd,ADJ}$	0.014 mg/kg/day	30	The chronic oral MRL is based on the same occupational study used to derive the chronic inhalation MRL where air samples were collected during a 16-month period. Average exposure duration was 6.1 years +/- 2.9 years. The study is discussed in more detail in the chronic inhalation study health effects. The human inhalation LOAEL of reduced WBC and platelet counts was converted to an equivalent oral dose of 0.29 mg/kg/day. Benchmark dose modeling identified a $BMCL_{0.25sd,ADJ}$ of 0.03 ppm (or 0.095 mg/m^3). Route to route extrapolation was then used to calculate an oral dose $BMDL_{0.25sd,ADJ}$ of 0.014 mg/kg/day. Health assessors should compare site-specific doses to the $BMDL_{0.25sd,ADJ}$ of 0.014 mg/kg/day when deciding the risk of reduced WBC and platelet counts. An analysis of reduced lymphocytes showed significantly decreased CD4+-T cells, CD4+/CD8+ ratio, and B cells, which are cells used to fight infection.	Lan Q, Zhang L, Li G, et al. 2004a. Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774-1776.

The PHAST database now contains study health effects for arsenic, benzene, trichloroethylene, tetrachloroethylene, and all forms of chromium. The PHAST database team continues to work on the top 20 chemicals and will let you know as more updates are completed.

The Dilemma of Evaluating Disinfectants, Disinfection Byproducts and Risk

Considerations for ATSDR health assessors when evaluating disinfectants and disinfectant byproducts

ATSDR health assessors often use routine public drinking water monitoring data in their health evaluations because public drinking water systems[1] can become contaminated from hazardous waste sources. In fact, many hazardous waste sites have been identified when routine water testing showed elevated levels of chemical contaminants that sparked further investigations. Public drinking water companies routinely test drinking water to comply with the federal Safe Drinking Water Act, thus generating a substantial set of data for health assessors to use.

- Although chemical disinfectants improve water quality by killing water-borne pathogens, they can also combine with organic material in the water to form disinfectant byproducts (DBP) many of which are possibly carcinogenic to humans.
    - The balance between having enough disinfectant to kill pathogens throughout an entire water distribution system and having too much is a challenge for water system operators because of the varying factors such as temperature, pH, total organic carbon, dissolved oxygen levels, natural organic matter, disinfectant levels, and in-line disinfectant time, which is the amount of time the water is in the municipal water distribution plumbing.
    - Combined cancer risk estimates for drinking water with more than one DBP chemical at the Maximum Contaminant Level (MCL)[2] can exceed the high end of US EPA's target cancer risk range of 1×10^{-4}.
    - CDC and World Health Organization consider the threat of waterborne pathogens to pose a real and more immediate threat to health than water disinfection by-products, ("lesser of these two evils") https://www.cdc.gov/safewater/chlorination-byproducts.html
- Unlike CERCLA chemical release evaluations, the addition of disinfectants and the resulting levels of DBP can fluctuate widely and the nuances of the rules are complex (e.g., using rolling annual averages for compliance). Therefore, it is not appropriate to use data that represents a snapshot in time to make hypothetical increase cancer risk estimates which assume a lifetime of excessive daily exposure.
- Consider evaluating disinfectants and DBP when a site has the following conditions:
    - The chemicals are site-related or the result of site-related chemical degradation or
    - Exposure to high chemical levels (typically from faulty pumps or mechanical failures) could result in acute gastrointestinal health effects such as nausea, vomiting, and diarrhea or
    - Consistently elevated levels of DBP above guidelines (noncompliance) occur over time and
- Our evaluation could help identify and improve public health practice (e.g., increase attention or resource allocation). In an evaluation write-up, include non-quantitative language that conveys the benefits of using disinfecting chemicals to kill germs that could cause sudden and severe illness such as cholera, typhoid, and dysentery far outweigh their estimated increase risk of cancer.

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[1] A public water system provides water for human consumption through pipes or other constructed conveyances to at least 15 service connections or serves 25 people or more for at least 60 days a year. A public water system may be publicly or privately owned.

[2] US EPA sets maximum contaminant levels (MCLs), which are the maximum permissible level of a contaminant in drinking water which is delivered to any user of a public water system. These levels are enforceable standards, which means that US EPA, Tribes, and states can take enforcement actions against water systems not meeting safety standards. https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=P100C8XW.txt

Soil Bioavailability Demystified

Health assessments often consider the potential for health effects from contaminants in soil that are accidentally swallowed. Usually only a portion of these contaminants get absorbed into the body (i.e. the body burden) while the remainder passes through the gastrointestinal tract and gets eliminated. The fraction of the contaminants absorbed is called the absolute bioavailability and is influenced by soil properties such as pH, chemical composition, and particle size.

Since health assessment involves the comparison of contaminant exposure from soil to that from a toxicity study, the relative bioavailability (RBA) is needed to calculate the body burden in a way that applies to the study. The RBA is the ratio of the absolute bioavailability from soil to the absolute bioavailability from the toxicity study. In health assessment, the RBA is multiplied by the dose to yield a bioavailable dose that can be compared to the critical dose from the toxicity study. Typically, the RBA is assumed to be 1 because we seldom have information about the absolute bioavailability for both the study and for soil.

Arsenic is an exception because the relative bioavailability of soil arsenic is well-studied. After conducting numerous site-specific *in vivo* swine studies and laboratory-based *in vitro* bioaccessibility (IVBA) assays, the U.S. EPA developed a default relative bioavailability for soil arsenic of 60% that is now automatically included in the PHAST dose calculator.

However, health assessors may sometimes be presented with site-specific IVBA studies for soil arsenic. The IVBA is determined by simulating gastric juices in the lab and measuring how much arsenic is extracted from site soil samples placed in the solution. U.S. EPA has used the paired laboratory and animal studies on mining, smelting, pesticide, industrial, and volcanic arsenic soils in the U.S. to develop a general *in vitro* to *in vivo* correlation (IVIVC). The IVIVC equation can be used with the soil arsenic IVBA results to derive a site-specific RBA to enter into PHAST. The ADS office is available to help review your site information to make sure it is applicable and to help document any limitations as needed. Here is the arsenic IVIVC equation:

RBA(%) = 0.79 * IVBA(%) + 3.0

Please consult with your ADS office for assistance with applying bioavailability results for other metals. The U.S. EPA has an IVIVC for lead, but we would like to review these on a case-by-case basis to best incorporate them into the overall lead assessment. DCHI has a 2019 Interim Guidance in PHAST for hexavalent chromium: *Using California EPA's Oral Cancer Potency Information for Hexavalent Chromium and Other Considerations*. It explains that the study used to derive the CalEPA CSF and the ATSDR MRLs were based on an administered dose, so health assessors should not apply bioavailability adjustments for chromium.

For further reading consult the following resources:

U.S. EPA: Soil Bioavailability at Superfund Sites (see the metals, arsenic, and lead sections)
https://www.epa.gov/superfund/soil-bioavailability-superfund-sites-guidance

ITRC: Bioavailability of Contaminants in Soil (see the case studies in chapter 11 for a quick overview)
https://itrcweb.org/teams/training/bcs

ATSDR SHOWER Model v2.0.0

On February 12, 2020, ATSDR released the SHOWER model v2.0.0, which replaces v1.0.4. V2.0 contains the same standard scenarios as v1.0 but allows the user more flexibility in changing model parameters and allows the user to evaluate exposure for households with up to 8 persons. Health assessors will still run the default scenario when making public health decisions about bathing in household water (Figure 1). Like v1.0, the v2.0 default scenario provides results for households with 1, 2, 3, and 4 persons and health assessors should use the results for the 4-person household to determine the risk of harmful effects.

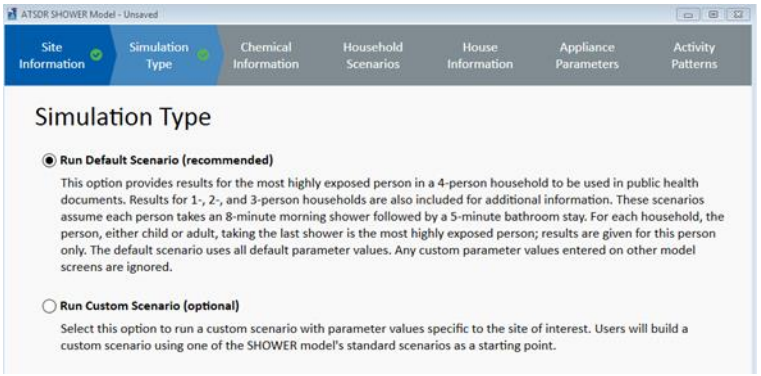

Figure 1. Simulation type screen where health assessors choose between running either the default or custom scenario.

Like v1.0, v2.0 also has the same ability to run built-in scenarios. These built-in scenarios, now for households with up to 8 persons, are part of the custom scenario option (Figure 1) and are selected on the Household Scenarios screen (Figure 2). You have the option of choosing all morning showers, a combination of morning and evening showers, as well as morning showers with evening baths—just like v1.0. Health assessors can use these built-in scenarios to understand the variation that might occur with different showering and bathing schedules and to answer questions from the community.

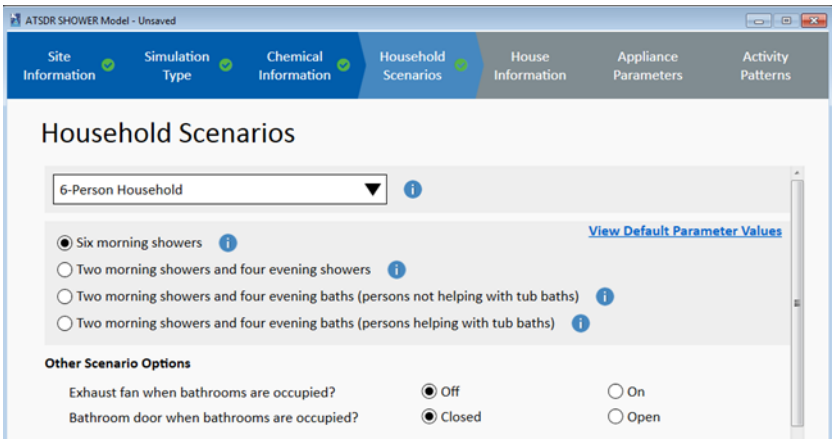

Figure 2. Built-in scenarios with various combinations of morning showers and evening showers or baths.

If you have questions or comments about ATSDR's SHOWER model, contact showermodel@cdc.gov.

What New DCHI Guidance is Evolving?

Do you know where to find all the latest FINAL DCHI guidance documents?

All of the latest guidance documents are posted in the Resources Section in PHAST. The table below shows new guidance coming soon!

Guidance Topics	Status	Point(s) of Contact
Exposure Point Guidance for Non-Discrete Sampling	Summer 2020	Greg Ulirsch; James Durant
Exposure Point Concentration (EPC) Guidance for PAHs	Summer 2020	Greg Ulirsch; James Durant
Exposure Unit (EU) Guidance	Spring 2020	Greg Ulirsch; James Durant
Air Exposure Dose Guidance	Summer 2020	Michelle Colledge