Mini-Module: Toxicological Evaluation

Agency for Toxic Substances and Disease Registry

Introduction to the Toxicological Evaluation

Module 7 teaches you that a toxicological evaluation is a step in the health effects evaluation. During this step, health assessors evaluate human exposure to a specific contaminant to determine whether people could become sick from their exposure. This evaluation guides ATSDR's recommendations to protect public health. A toxicological evaluation is conducted under the following conditions:

- Site-specific hazard quotients (HQs) exceed 1.
- Site-specific cancer risks (CRs) exceed 1E-06.
- No health guideline is available to evaluate non-cancer effects for a contaminant.
- No oral cancer slope factor (CSF) or inhalation unit risk (IUR) is available for a known or suspected carcinogen.
- A contaminant is a community concern.
- Other factors (such as concerns about specific sensitive populations) warrant further evaluation (even if no HQs or CRs were above acceptable levels).

Introduction to the Toxicological Evaluation (cont.)

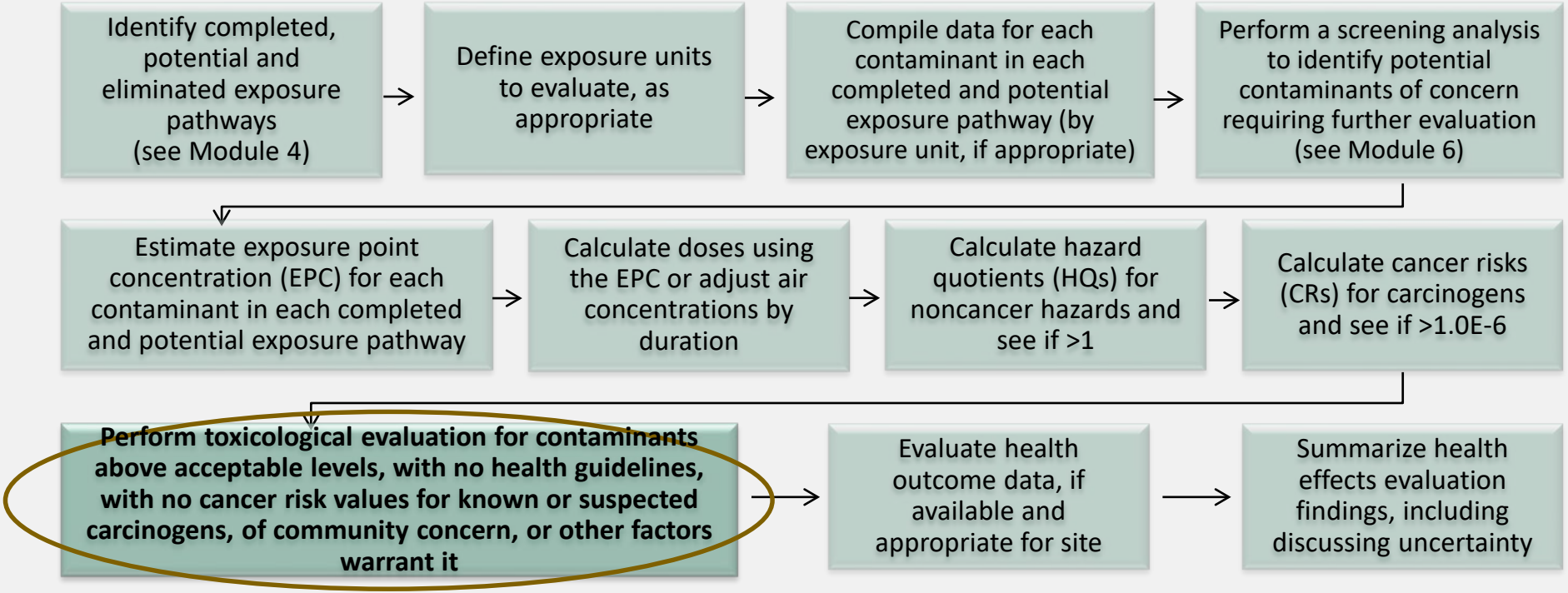
This mini-module contains detailed information you need to know before performing a health effects evaluation.

Let's take a look at the public health evaluation process, and see where the topic in this mini-module — the toxicological evaluation — fits in. As you will see, this part of the process is circled in the flow chart on the next page. The topic of conducting the toxicological evaluation is Step 7 in Module 7.

Important: The values and reference documents used in this mini-module were current when this training was developed. These can be updated periodically, so be sure to use the most current information at your real sites.

Steps of the Public Health Evaluation Process

This figure shows the overall steps involved in ATSDR's public health evaluation.



Steps of the Public Health Evaluation Process (cont.)

It is important to remember that the PHA process has many steps. Typically, the four primary technical components involve evaluations of 1) exposure pathways, 2) screening analyses, 3) EPCs and exposure calculations, and 4) in-depth toxicological effects.

The sequence of steps laid out in the previous figure may differ slightly, depending on site-specific factors. For instance, health assessors may define an exposure unit before or after the screening analysis. With large data sets, the health assessor may decide to complete the media-specific screening on the entire data set to identify potential contaminants of concern at the site, and then define appropriate exposure units for further analysis.

For smaller or more defined data sets, the health assessor may decide to define the exposure units before the screening analysis. Health assessors will use professional judgement to decide when to define exposure units; however, they must define them before determining EPCs.

What Questions Will the Toxicological Evaluation Help Me Answer?

In the public health assessment (PHA) process, a toxicologic evaluation includes reviewing information to answer questions such as the following:

- How does the contaminant get into the body?
- What happens to the contaminant after it gets into the body?
- What data were used to develop the health guidelines and cancer risk values?
- What effects are associated with the contaminant and at what doses or concentrations?
- How do site-specific doses or concentrations compare to health effects doses or concentrations in published studies?

The main overall steps of the process are outlined in the next image. After you review that, we'll get started.

When to Conduct a Toxicological Evaluation

Perform toxicological evaluations to examine contaminants that meet any of the following criteria:

- Yield HQs >1
- Yield CRs >1E-06
- Have no non-cancer health guidelines
- Have no cancer risk values for known or suspected carcinogens
- Are a community concern
- Have factors that warrant further evaluation, even if no HQ/CR exceedances

Main Steps of the Toxicological Evaluation

1. Identify data from key studies used to develop *non-cancer* health guidelines.
2. Review the original journal article(s) that served as the basis for the *non-cancer* health guidelines and more recent studies, if needed.
3. Evaluate the evidence to examine *non-cancer* effects.
4. Evaluate the evidence to examine *cancer* effects.
5. Review toxicological information for other health effects (target organs and systems) with doses or air concentrations like those for your site. Compare site doses or air concentrations to the Levels of Significant Exposure (LSE) tables/figures in the ATSDR Toxicological Profile.
6. Review other contaminant-specific information that might influence a decision about whether harmful effects are possible.
7. Consult with a team toxicologist or epidemiologist to help interpret or identify information.

Approach for the Toxicological Evaluation Discussion

Throughout this mini-module, we will explain what is involved in each step of the toxicological evaluation process.

After you learn about each step, we will use our case study example to demonstrate how to perform that step. This is similar to what we did in other steps of Module 7.

When we are going to do an example, those slides will say “Practice” in the title. For practice, we will walk through each step using our class exercises from previous steps in Module 7, where we identified certain exposure scenarios requiring further evaluation in the toxicological evaluation.

Approach for the Toxicological Evaluation Discussion (cont.)

As you recall from the previous steps (Steps 1–6) in Module 7, we identified certain exposure scenarios from our training exercises that required a toxicological evaluation. We will evaluate those here.

- First, we will practice together. We will conduct a toxicological evaluation for the estimated exposure doses and cancer risks for residents drinking carbon tetrachloride contaminated water from PW-3 over a chronic duration that exceeded HQs of 1 and CRs of 1.0E-6, respectively.

- Then, you will do a case study exercise. You will conduct a toxicological evaluation for estimated exposure doses and cancer risks associated with arsenic in soil at the daycare that exceeded HQs of 1 and CRs of 1.0E-6, respectively. In addition, a toxicological evaluation is needed to evaluate the intermediate pica exposures, because no intermediate duration health guideline is available.

Resources to Support the In-Depth Analysis

There are several information sources you will use during the in-depth analysis. The most common sources of these data are listed below. For definitions of these terms, refer to the Glossary on the PHAT home page.

- ATSDR's Contaminant-specific Toxicological Profiles
- CVs & Health Guidelines module *(in ATSDR's Public Health Assessment Site Tool [PHAST])*
- EPA's Integrated Risk Information System (IRIS) Database
- International Agency for Research on Cancer (IARC) Monographs
- National Toxicology Program (NTP)
- National Library of Medicine's (NLM's) databases (PubChem, PubMed)
- Peer-reviewed scientific journals
- Standard toxicology textbooks

Identify Data from Key Studies

Now, let's learn about the first step in the toxicological evaluation process, which is to review the basis for the study or studies used to derive the health guideline (such as the minimal risk level [MRL] or reference dose [RfD]).

If no MRL, RfD, RfC, or other acceptable non-cancer health guideline is available, you will compare your site-specific doses or concentrations directly to those in animal and human studies based on the same exposure duration to determine the risk of harmful effects (we will show you this process later in this mini-module).

Important: Health assessors need to examine key studies when a non-cancer health guideline is exceeded, but this is not a required step when a cancer risk estimate exceeds a level of concern. For cancer risk, health assessors are only required to quantitatively estimate the cancer risk (when a contaminant has an oral cancer slope factor [CSF] or an inhalation unit risk [IUR]) and interpret that risk. In rare cases, it could be useful to review the original study. Consult with an ATSDR toxicologist if you need assistance.

Identify Data from Key Studies (cont.)

When using the available information sources, you will likely see some terms that are new to you. We will go over a few terms here, but we won't have time to define many of them. Please refer to the "List of Toxicology Terms Related to Health Guidelines", as well as the "Glossary" and "List of Acronyms" in the training Resources section for more information.

Identify Data from Key Studies (cont.2)

The observed effect levels, including the following, are used to develop health guidelines :

- **NOAELs (no-observed-adverse-effect levels):** These are the highest dose level (below the LOAEL) at which no adverse or toxic effect has been observed.
- **LOAELs (lowest-observed-adverse-effect levels):** These are the lowest dose level at which an adverse or toxic effect has been observed.
- **BMDL/BMCL:** This is the lower bound of the confidence interval for the benchmark dose (BMD) or benchmark concentration (BMC). It is the lower confidence limit that corresponds to a dose or concentration that produces a specific magnitude of changes for a particular adverse response.
- **HED/HEC:** The human equivalent dose or concentration. Exposures are converted to their human equivalents if possible (through the use of toxicological models).

Identify Data from Key Studies: Practice

Now, we will practice together using our carbon tetrachloride in drinking water case study example. Before we start, it might help to look at the steps for this example exercise in Module 7 that came before this Step 7:

- *Step 1: Define exposure units to evaluate.* You defined the exposure units — the six drinking water wells (PW-1 through PW-6). For our example, we are using PW-3.
- *Step 2: Compile data for each exposure unit.* For the purposes of this example, we are focusing on the one potential COC that exceeded its CV during the screening (Module 6), carbon tetrachloride, and one exposure pathway, drinking water ingestion. The carbon tetrachloride data for PW-3 are summarized in the table here.

Carbon tetrachloride sampling results in parts per billion (ppb) for PW-3 by sampling date

1/15	3/15	5/15	6/15	7/15	8/15	9/15	10/15	11/15	12/15
280	260	275	190	210	180	220	290	265	230

Practice (cont.)

- *Step 3: Estimate the EPC.* As you learned in the EPC mini-module, the EPC to evaluate intermediate and chronic exposures for the carbon tetrachloride case example scenarios is the 95UCL of 262.7 ppb.

- *Steps 4: Calculate doses, Step 5: Calculate HQs for noncancer hazards to see if >1, and Step 6: Calculate CR estimates to see if >1.0E-6.* In Module 7, we used PHAST to perform these steps to obtain exposure estimates. For the toxicological evaluation, we will evaluate the HQs and CRs that exceeded these guidelines for the chronic exposure scenario. See the PHAST results table on the next page, which was from these steps in Module 7 for the chronic exposure scenario that used all default exposure parameters. [Note: There were no HQ or CR exceedances for the site-specific intermediate exposure scenario for the house guest, so that doesn't require a toxicological evaluation.]

Practice (cont.2)

Default Residential Results for Standard Age Groups

● Standard Child Age Group ▲ Standard Adult Group ■ Special Group ◆ Screening Cancer Risk

− Chronic Exposure

Exposure Group	Default Residential Scenario							
	Chronic Dose (mg/kg/day)		Chronic Hazard Quotient		Cancer Risk §			
	CTE	RME	CTE	RME	CTE	ED (yrs)	RME	ED (yrs)
− **CARBON TETRACHLORIDE (EPC: 0.2627 mg/L; Chronic RfD: 0.004 mg/kg/day; CSF: 0.07 (mg/kg/day)$^{-1}$)**								
● Birth to < 1 year	0.017	0.037	4.2 †	9.4 †	6.4E-5 ‡	1	2.4E-4 ‡	1
● 1 to < 2 years	0.0071	0.021	1.8 †	5.1 †		1		1
● 2 to < 6 years	0.0057	0.015	1.4 †	3.7 †		4		4
● 6 to < 11 years	0.0042	0.012	1.1 †	2.9 †		5		5
● 11 to < 16 years	0.0029	0.0091	0.74	2.3 †		1		5
● 16 to < 21 years	0.0028	0.0090	0.71	2.2 †		0		5
● Total exposure duration for child cancer risk						12		21
▲ Adult	0.0040	0.010	1.0 †	2.5 †	4.3E-5 ‡	12	3.0E-4 ‡	33
■ Pregnant Women	0.0031	0.0093	0.78	2.3 †	NC Ω			
■ Lactating Women	0.0060	0.013	1.5 †	3.2 †	NC Ω			
◆ Birth to < 21 years + 12 years during adulthood	*Do not use this cancer risk unless you have a scenario where children are likely to continue to live in their childhood home as adults.*						3.5E-4 ‡	33

Practice (cont.3)

- Now, you're ready to conduct the toxicological evaluation (Step 7). We will practice together using our carbon tetrachloride in drinking water exposure scenarios.

- Let's dive in. Let's first take a look at the ATSDR Toxicological Profile for Carbon Tetrachloride to get a sense of the information ATSDR is reporting. The profile states: "No data were located on the effects of chronic-duration oral exposure in humans." Also, "Since a no-effect level was not identified and ATSDR does not base MRLs on doses at which serious effects occur, a chronic duration oral MRL was not derived for carbon tetrachloride."

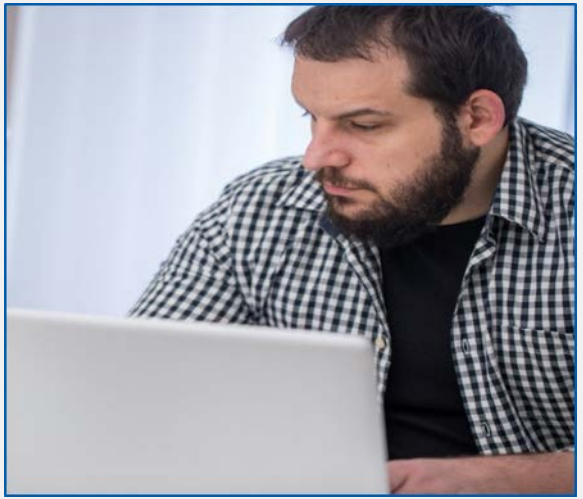
Practice (cont.4)

- We know from our example that PHAST is using the EPA RfD for calculating HQs to evaluate non-cancer effects from chronic oral exposure to carbon tetrachloride. This is one example of when ATSDR and EPA differ in their approaches, whereby ATSDR didn't develop a chronic MRL based on available data, but EPA used a sub-chronic study to develop a chronic RfD.

With some exceptions, if ATSDR has an MRL and EPA has an RfD for the same contaminant, ATSDR usually uses its MRL. PHAST will automatically select the most appropriate value.

Practice (cont.5)

Now, let's take a look at EPA's IRIS Assessment for Carbon Tetrachloride. Here, we can review the IRIS Summary and the Toxicological Review. IRIS will be our source for data from key studies that EPA uses to develop the health guidelines that apply to our example: RfD for non-cancer effects. We can also look in the ATSDR Toxicological Profile for additional contaminant-specific information.



The table on the next page will be your guide for pulling data from the source documentation. We have reviewed the IRIS information, looked at the ATSDR Toxicological Profile, and filled in the table for you.

Important: The contaminant-specific information being used in the next table is for training purposes only. Also, as mentioned, ATSDR, EPA, and other agencies update their values periodically. Be sure that you always use the most current values and supporting information from key studies in your evaluation.

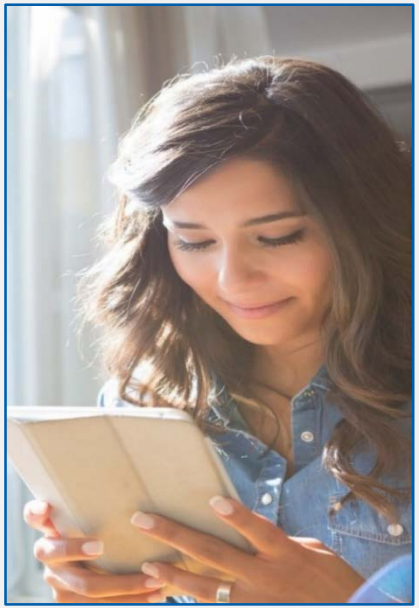
Practice (cont.6)

Identify data from key studies for non -cancer effects—carbon tetrachloride

Parameter	Data for Non-cancer Health Effects
Health guideline value	RfD: 0.004 mg/kg/day
Information source	EPA IRIS
Study reference for health guideline	Bruckner et al., 1986
Exposure route and duration evaluated	Oral, subchronic
No-observed-adverse-effect level (NOAEL), if one was reported (include units)	1 mg/kg/day
Lowest-observed-adverse-effect level (LOAEL), if one was reported (include units)	10 mg/kg/day
Observed effect	Elevated serum sorbitol dehydrogenase (SDH) activity (biomarker of liver toxicity)
Species LOAEL/NOAEL/BMDL is based on	Rats
Dosing method and exposure medium	Oral gavage in corn oil
Point of departure	$BMDL_{2X\text{-}ADJ}$: 3.9 mg/kg/day
Uncertainty factors (UF)	1,000

$BMDL_{2X\text{-}ADJ}$ = 95% confidence limit on the benchmark dose corresponding to an increase in SDH activity two times the control mean (this BMDL accounts for an adjustment (*5/7) so it would represent an average daily dose)

Review Articles, if Needed



This step involves reviewing original journal article(s) that were the basis for the health guidelines, and studies published more recently than those used to derive the health guidelines.

Based on the Toxicological Profile, we know ATSDR did not find an appropriate study for the basis of a chronic MRL, but EPA found a sub-chronic study that it used to develop its chronic RfD. Looking at the data from the key studies table we just completed, we see that the RfD is based on Bruckner et al., 1986.

For this example, we can have confidence in this study because EPA found it appropriate to use to support the development of the RfD.

However, at your real sites, you might still have questions about the health guideline and want additional information not found in ATSDR's Toxicological Profile or EPA's IRIS. In that case, if you deem warranted, you could review the original journal article(s) that were the basis for the health guideline to gain more insight into the study. These journal articles are available to ATSDR staff and its partners through DocExpress.

Review Articles, if Needed (cont.)

Now, if warranted for real sites, you may need to identify studies published more recently than those used to develop the health guidelines. For example, you may have a high-profile contaminant, or a contaminant has a toxicological profile that is out for public comment. In these cases, you may want to talk to the ATSDR profile manager to see if there are more recent studies that could be useful.

Make sure to clearly identify any newer information you use in your report as being from a more recent publication. Because we have limited time here, we won't do that for our example. While not required, you may wish to search for more recent articles.

Review Articles, if Needed (cont.2)

Some example sources are listed below.

Sources with free public access:

- ATSDR's Toxicological Addendums
- PubMed
- Google Scholar

Resources requiring CDC account access:

- CDC stacks, public health publications
- Doc Express (to access free articles)

Introduction to the Process for Evaluating the Toxicological Evidence

Health assessors will use different approaches to evaluate non-cancer effects versus cancer effects, but both include evaluating the available toxicological evidence. After we talk about evaluating the evidence, we will summarize the different approaches for evaluating non-cancer and then talk about cancer effects.

What is the Process for Evaluating the Toxicological Evidence?

This process is aimed at evaluating the available evidence — in light of uncertainties — and giving an overview of whether noncancer and cancer health effects are likely or not likely under site-specific exposure conditions.

Health assessors will consider various factors in the evaluation, such as the following:

- *Quality of the study (note: we know a study used by ATSDR or EPA to develop a health guideline was already determined to be of good quality; here you can assess whether your site-specific exposure conditions and the study design are sufficient for making decisions about harmful health effects)*

- *Relevance of critical study to site-specific scenario*

Let's talk about how examining the evidence fits into the approach for evaluating non-cancer and cancer effects, and do examples using our case study example.

Evaluate the Evidence: Non-Cancer

Steps for *Non-cancer* Effects

Now, to evaluate non-cancer effects, we will see how our site-specific example exposure doses compare with the observed effect levels used to generate the health guidelines. The purpose of this step is to determine where your site-specific doses or concentrations lie in relation to the observed effect levels (such as NOAELs and LOAELs) reported in the critical studies. We also want to see if differences between the study data and exposure scenario you are evaluating make health effects more or less likely.

Two key steps in this analysis are to

1) compare site-specific exposure doses or concentrations (based on the EPC) with effect levels observed in the critical study (NOAEL, LOAEL, BMDL, HED, or similar toxicologic term), and

2) carefully consider study parameters in the context of site exposures.

Evaluate the Evidence: Non-Cancer (cont.)

Steps for *Non-cancer* Effects (continued)

- For *noncancer effects only*, you may consider numerically comparing the site-specific doses or concentrations to the study's health effect doses or concentrations. In addition to directly comparing the values, health assessors can determine how close the site-specific doses or concentrations are to doses or concentrations associated with an effect. This comparison is done by dividing the critical study's NOAEL, LOAEL, BMDL, or HED (as reported in Appendix A of the Toxicological Profile or IRIS) by the site-specific exposure dose or concentration. Thus, an example equation using the LOAEL would be LOAEL / site-specific exposure dose.

Evaluate the Evidence: Non-Cancer (cont.2)

Steps for *Non-cancer* Effects (continued)

- Comparison to levels where effects were observed (such as HEDs or BMDLs) is preferred
  to NOAELs.
- The resulting value is often referred to as a margin-of-exposure (MOE).
- ATSDR does not have a specific scheme to determine the confidence (such as low, medium, high) in the MRL, the study, or the health endpoints. Health assessors should use information from the toxicological profile and IRIS, as well as the evaluation of evidence and professional judgment, when deciding whether non-cancer health effects might be possible.

Evaluate the Evidence: Non-Cancer (cont.3)

Steps for *Non-cancer* Effects (continued)

- When there is no health guideline for a contaminant, you can also use this process to compare your site-specific doses or concentrations directly to those in animal and human studies to determine the potential for harmful health effects.
- Consider consulting a toxicologist during your evaluation, such as which effect level is appropriate to use.

Evaluate the Evidence: Non-Cancer, Practice

Now, let's do one of the steps you just learned by comparing our example site-specific dose for carbon tetrachloride to the lowest LOAEL in the study that served as the basis for the *non-cancer* health guideline.

The highest chronic exposure dose in our case exercise, RME for ages birth to <1 year, was estimated to be 0.037 mg/kg/day. We will use this in our example. Per EPA IRIS, the oral subchronic 12-week study used for the basis of EPA's RfD reported a benchmark dose lower confidence limit (BMDL) of 3.9 mg/kg/day.

To perform a numeric comparison of the health effect study levels and the site doses (also called MOE), let's use the BMDL for our example. We would divide the BMDL of 3.9 mg/kg/day by 0.037 mg/kg/day, where 3.9 / 0.037 = 105. This means the highest site-specific exposure dose from our case example is 105 times lower than the BMDL, the lowest estimated to show effects in animals exposed.

Let's look next at *cancer* effects.

Evaluate the Evidence: Cancer

Now, we will discuss how to evaluate the evidence to examine *cancer* effects.

Steps for *Cancer* Effects

- For *cancer* effects, ATSDR uses the information gathered from the exposure pathway analyses and exposure estimates to get a range of cancer risks that represent typically and highly exposed groups.
- Health assessors estimate the theoretical increased risk of cancer in an exposed population by multiplying the site-specific exposure dose estimate by the oral CSF or the site-specific air concentration by
  the IUR.
- Health assessors will need to discuss the types of cancer that might be possible and should keep in mind that some cancers might be route specific.

Evaluate the Evidence: Cancer (cont.)

Steps for *Cancer* Effects (continued)

- Do not conduct a comparison between the cancer effect level (CEL-the lowest dose level observed to produce a significant increase in the incidence of cancer or tumors) and site exposure dose to assess cancer effects.

  This is because cancer risk is a linear response without a threshold and very low doses can still cause an increased risk of cancer.

- Do not use a CEL to make a health hazard conclusion.

  This is because you need to know the numerical cancer risk to decide whether exposure could cause a significant cancer risk.

Evaluate the Evidence: Cancer (cont.2)

Steps for *Cancer* Effects (continued)

- When communicating the potential for cancer hazards, be sure to state how strongly associated a contaminant is with cancer outcomes. Using plain language, include the cancer classifications in your evaluation (look at PHAST for agency-specific classifications) to describe the cancer-causing potential of a contaminant.
- A decision on whether there is a potential for cancer effects will call for professional judgement. Request toxicological assistance to help with these types of evaluations.

Evaluate the Evidence: Cancer (cont.3)

Steps for *Cancer* Effects (continued)

- For suspected or known carcinogens that don't have CSFs or IURs, health assessors need to indicate in their documents that quantitative risk estimates aren't possible. Provide some context in your documents as noted below.
  - Include highlights from studies supporting the contaminant being a carcinogen.
  - Include information on how you identified the contaminant as a carcinogen (e.g., NTP or IARC cancer classification).

Evaluate the Evidence: Cancer (cont.4)

Steps for *Cancer* Effects (continued)

- Indicate what is known in a qualitative way. Provide a paragraph that explains why EPA hasn't developed CSFs or IURs based on available data (if known), clearly states uncertainty, and includes other relevant information.
- Note that cancer risk estimates do not estimate actual cancer cases, but rather provide information to ATSDR when making determinations about actions needed to protect the public's health.
- Consult with a toxicologist if there is information on human or animal exposure doses that caused cancer to see if it is appropriate to compare them to site-specific doses.

Evaluate the Evidence: Cancer, Practice

Let's look at examples of information we might collect to examine potential cancer effects using our carbon tetrachloride example. This information is found in the ATSDR Toxicological Profile, EPA IRIS, and ATSDR Health Guidelines and Cancer Risk table (for the cancer classifications). You would pull all relevant information at your real sites. The next slide is a table with types of information you might want to gather, using the carbon tetrachloride example. We examined and collected information for these factors:

- *Quality of study*: we know a peer-reviewed study was deemed sufficient by EPA to use for the basis of an oral CSF, but the study used a relatively small group size and investigation of only two target organs (kidney and liver)
- *Cancer classification of contaminant*: LC-likely to be carcinogenic to humans (EPA), 2-reasonably anticipated to be a carcinogen (NTP), 2B-possibly carcinogenic to humans (IARC), and OC-occupational carcinogen (NIOSH)

Cancer, Practice (cont.)

Identify data from key studies and other information for cancer effects – carbon tetrachloride

Parameter	Data for Cancer Effects
Cancer risk value	CSF: 0.07 mg/kg/day^{-1}
Information source for cancer risk value	EPA IRIS (Toxicological Profile for CEL)
Study reference	JBRC, 1998; Nagano et al., 2007
Study exposure route and duration evaluated	Inhalation, chronic
Observed effect for cancer risk value	Liver cancer (hepatocellular adenoma or carcinoma)
Species cancer risk value is based on	Mice
Dosing method and exposure medium in study	Inhalation bioassay
Point of departure in study	LED_{10}: 1.54 mg/kg/day
Cancer classification(s)	LC-likely to be carcinogenic to humans (EPA), 2-reasonably anticipated to be a carcinogen (NTP), 2B-possibly carcinogenic to humans (IARC), and OC-occupational carcinogen (NIOSH)

LED_{10} = the lower 95% bound on the exposure associated with a 10% extra cancer risk; the CSF is obtained by dividing the risk (as a fraction) by the LED_{10}

Review Other Health Effects for Similar Doses

In this next step, you will review studies for other health effects (target organs and systems) with doses or air concentrations similar to those doses or air concentrations for your site.

When a Toxicological Profile is available for a potential COC, health assessors should use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, HEDs, HECs, BMDLs, or CELs. Also, when making decisions about health effects, you should always read the information provided in the MRL worksheet (Appendix A in the Toxicological Profiles).

Review Other Health Effects for Similar Doses (cont.)

For reference, the doses from our example are shown here, and the doses from the LSE tables/figures (NOAELs, LOAELs, etc.) are shown in upcoming slides. You will focus on comparing the highest site dose, which was estimated to be 0.037 mg/kg/day for our chronic exposure example.

● Standard Child Age Group ▲ Standard Adult Group ■ Special Group ◆ Screening Cancer Risk

− Chronic Exposure

Exposure Group	Default Residential Scenario							
	Chronic Dose (mg/kg/day)		Chronic Hazard Quotient		Cancer Risk §			
	CTE	RME	CTE	RME	CTE	ED (yrs)	RME	ED (yrs)
− CARBON TETRACHLORIDE (EPC: 0.2627 mg/L; Chronic RfD: 0.004 mg/kg/day; CSF: 0.07 (mg/kg/day)$^{-1}$)								
● Birth to < 1 year	0.017	0.037	4.2 †	9.4 †	6.4E-5 ‡	1	2.4E-4 ‡	1
● 1 to < 2 years	0.0071	0.021	1.8 †	5.1 †		1		1
● 2 to < 6 years	0.0057	0.015	1.4 †	3.7 †		4		4
● 6 to < 11 years	0.0042	0.012	1.1 †	2.9 †		5		5
● 11 to < 16 years	0.0029	0.0091	0.74	2.3 †		1		5
● 16 to < 21 years	0.0028	0.0090	0.71	2.2 †		0		5
● Total exposure duration for child cancer risk						12		21
▲ Adult	0.0040	0.010	1.0 †	2.5 †	4.3E-5 ‡	12	3.0E-4 ‡	33
■ Pregnant Women	0.0031	0.0093	0.78	2.3 †	NC Ω			
■ Lactating Women	0.0060	0.013	1.5 †	3.2 †	NC Ω			
◆ Birth to < 21 years + 12 years during adulthood	*Do not use this cancer risk unless you have a scenario where children are likely to continue to live in their childhood home as adults.*						3.5E-4 ‡	33

Review Other Health Effects for Similar Doses (cont.2)

ATSDR's Toxicological Profiles use LSE tables and figures to summarize the exposure doses and concentrations associated with health effects reported in scientific studies.

These levels cover

- health effects observed at different doses or concentrations and durations (acute, intermediate, and chronic),
- differences in response by species,
- the study used to derive duration-specific MRLs,
- CELs from animal and human studies, and
- EPA's estimated range for doses and concentrations associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 1,000,000 (when CSFs or IURs are available).

Review Other Health Effects for Similar Doses (cont.3)

After you've found the LSE tables and figures in the Toxicological Profile, compare your site doses or concentrations with those from the studies provided. This is a simple step that can really provide perspective of where your site-specific doses or concentrations fall in relation to those seen in published scientific studies.

As we learned, ATSDR has no chronic MRL for carbon tetrachloride because the chronic oral studies identified were based only on serious effects. But there is a chronic oral exposure LSE table and figure in the Toxicological Profile that lists the studies that were available. So, let's take a look at them so you will know how to use the LSE tables and figures for your sites.

Review Other Health Effects for Similar Doses: Practice

Here's the LSE table. For our case exercise, the highest chronic exposure dose was estimated to be 0.037 mg/kg/day. This table has no NOAEL, and the lowest LOAEL is 47 mg/kg/day. This is 1,270 times higher than our dose, but it's *very important to note* that this dose is for a serious LOAEL.

Table 3-2 Levels of Significant Exposure to Carbon Tetrachloride - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
57	Rat (Osborne-Mendel)	78 wk 5d/wk (G)				94 M (survival at 110 wks decr by 46%)	NCI 1976
58	Mouse	78 wk 5d/wk (G)				1250 (survival decr by 80%)	NCI 1976
Systemic							
59	Rat (Osborne-Mendel)	78 wk 5d/wk (G)	Hepatic			47 M (cirrhosis, bile duct proliferation, fatty accumulatioin)	NCI 1976
Cancer							
60	Rat	78 wk 5d/wk (G)				47 M (CEL: hepatocellular carcinomas)	NCI 1976
61	Mouse (B6C3F1)	78 wk 5d/wk (G)				1250 (CEL: 100% with hepatic carcinoma)	NCI 1976

Review Other Health Effects for Similar Doses: Practice (cont.)

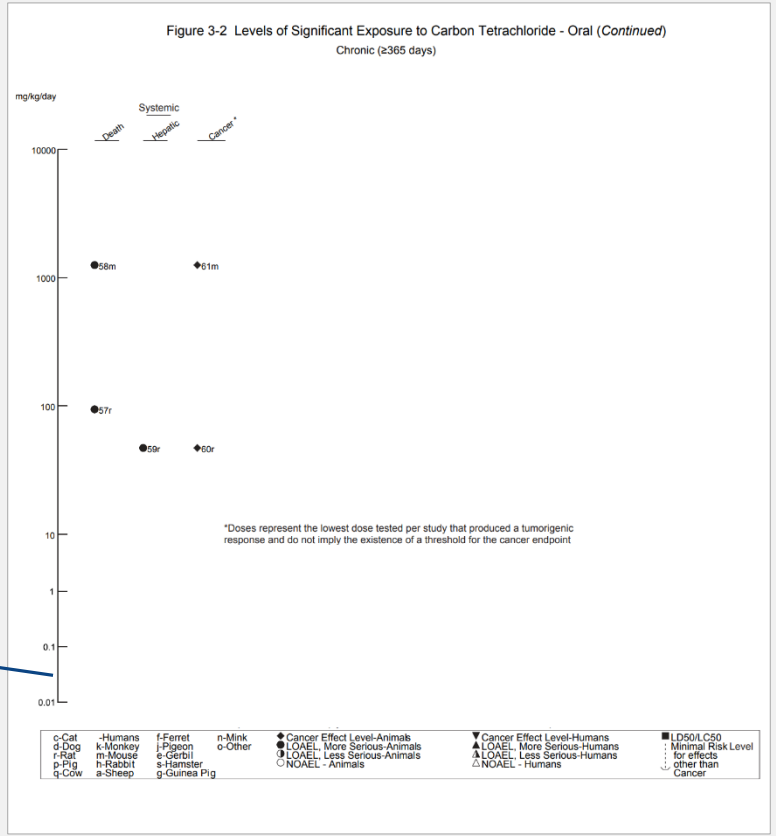
For training purposes, the LSE figure on the next page has been modified from the original figure in the Toxicological Profile. Again, for our case exercise, the highest chronic exposure dose from drinking carbon tetrachloride contaminated water was estimated to be 0.037 mg/kg/day. The LSE figure is helpful to see where your site-specific doses compare with those in the published studies.

You can see that our example dose is several magnitudes lower than the doses where effects were noted in the chronic, oral scientific studies reported on the Toxicological Profile LSE table. But again, the reported levels in the LSE table are based on serious effects — a dose for a less serious LOAEL could be much lower than those reported here.

Review Other Health Effects for Similar Doses: Practice (cont.2)

Compare site doses to the LSE Tables/Figures in the ATSDR Toxicological Profile.

Our example dose of 0.037 mg/kg/day would fall about here



Review Other Health Effects

For contaminants without an ATSDR Toxicological Profile, we recommend that you refer to the EPA IRIS Toxicological Reviews. Health assessors may also want to refer to EPA IRIS if the Toxicological Profile available for their contaminant was completed before EPA derived the RfD.

Also, even though a Toxicological Profile is available for our potential COC, our health guideline and cancer risk value are from EPA. At a real site, we would go to the EPA IRIS Toxicological Review next to see if there is more information that we might be interested in. Here, you will find tables to see where your doses fall compared to the doses EPA pulled from all the studies examined during its health guideline and cancer risk value development. For example, you might find a table that summarizes chronic and sub-chronic oral toxicity studies, such as Table 4–13 in EPA's IRIS Toxicological Review for Carbon Tetrachloride.

Review Contaminant-Specific Toxicological Information

Here, you will examine the available toxicological information to see if there is anything about your contaminant that could influence whether exposures could result in harmful effects. There are various types of information to consider, such as:

- *Toxicokinetics* (*absorption*, *distribution*, *elimination*, *metabolism*)
- *Mechanisms of action*
- Children's *susceptibility*, including *mutagenicity*
- Populations that are unusually susceptible
- *Interactions* with other contaminants
- General population and population with more than average exposure

Note: Typically, health assessors will find the contaminant-specific information they need in previously published ATSDR documents. You can use this information in your written materials after checking that it is up-to-date.

Review Contaminant-specific Toxicological Information (cont.)

Now, we'll examine our two main toxicological information sources for our potential COC — the *Toxicological Profile* and *EPA IRIS* — and show some examples of the type of information you might pull for this step (see next pages).

It is important to note that we will not be presenting a full list of all the information you might collect or all the sources that might be available. For training purposes, we will show examples of information we might consider based on our COC and drinking water ingestion (oral) scenario. At real sites, the information to collect will vary by your COCs, exposures, and concerns.

If you have questions during your evaluation, always reach out to a team toxicologist for assistance.

Review Contaminant-specific Toxicological Information: Practice

We pulled the following information for carbon tetrachloride using our ATSDR and EPA sources:

1. Readily absorbed (about 85%-91%) through the gastrointestinal tract from oral exposure.
2. Largest fraction of an absorbed oral dose initially distributed to fat, but then traveled to blood, muscle, liver, and brain.
3. Metabolized mainly by the liver, but also other tissues, such as the lung and kidney.
4. Most leaves the body unchanged, but some can change to other contaminants before leaving the body.
5. Leaves the body in expired air, feces, and urine. May take weeks for some to be eliminated, especially if stored in body fat.

Review Contaminant-specific Toxicological Information: Practice (cont.)

6. Metabolism of carbon tetrachloride is required for toxicity.
7. Children are expected to have similar health effects from exposure via drinking water ingestion (pathway for this example) as adults (not increased susceptibility).
8. Possible exposure of infant via breastfeeding, but exposure levels likely to be low.
9. Evidence suggests toxicity is dramatically increased by interactions with alcohols, ketones, and a variety of other contaminants.
10. Moderate to heavy drinkers are at significantly increased risk of liver and/or kidney injury following ingestion.
11. Fetuses of mothers who drink alcohol would potentially be more susceptible to exposure.

Consult Team Toxicologist or Epidemiologist to Help Interpret or Find Information

- Seek the expertise of a toxicologist if you need help looking for or interpreting any of the toxicological information you've collected.
- For contaminants with no health guidelines or no cancer risk values for known or suspected carcinogens, consult with the toxicologist, epidemiologist, or other SME on your team to review the most current dose-response data and the status of any pertinent research. If you identify limited or no data, review the site-specific exposure potential, and determine whether the absence of toxicity data is a critical data gap to assessing the possibility of site-related health effects.

Summary of Health Effects Evaluation

Now, let's summarize the toxicological evaluation results for our case exercise on carbon tetrachloride. We might have something like this:

Non-cancer Health Effects

- The oral sub-chronic 12-week study used for the basis of the EPA's RfD reported a BMDL of 3.9 mg/kg/day. This means that the highest site-specific exposure dose from our case example (0.037 mg/kg/day) is 105 times lower than the BMDL, the lowest level estimated to show effects in animals exposed to carbon tetrachloride.
- We are confident in using EPA's RfD to assess non-cancer effects for our site. EPA performs many scientifically defensible steps to derive its values, and as such, ATSDR approves of their use in the public health assessment process.
- We must, however, consider there is some uncertainty with comparing a chronic (1 year or longer) exposure dose to one based on a study conducted over a shorter, sub-chronic duration. Also, EPA acknowledges other limitations of the study, such as relatively small group size and evaluation of only two target organs (kidney and liver).

Summary of Health Effects Evaluation (cont.)

Non-cancer Health Effects (continued)

- After a consideration of the uncertainty and a review of all the scientific data available, ATSDR is confident in comparing the estimated dose to this BMDL.
- Based on this dose comparison and evaluating the evidence, ATSDR believes that the detected levels of carbon tetrachloride are not likely to harm PW-3 residents under the site-specific conditions evaluated.

Summary of Health Effects Evaluation (cont.2)

Cancer Health Effects

- EPA's cancer assessment of carbon tetrachloride includes some uncertainties, such as modeling being used to estimate the oral slope factor. Even so, EPA indicates that available evidence supports the conclusion that experimental findings of liver cancer seen in animals are relevant to humans.

- It is important to provide additional perspective on ATSDR's estimated carbon tetrachloride increased cancer risk of 2 to 3 extra cancer cases per 10,000 people. For instance, the American Cancer Society (2018) reports that 4,000 out of 10,000 U.S. men and 3,800 out of 10,000 U.S. women will develop cancer at some point in their lifetime.

Summary of Health Effects Evaluation (cont.3)

Cancer Health Effects (continued)

- ATSDR's evaluation suggests that drinking the carbon tetrachloride contaminated water from PW-3 for many years results in an increased lifetime risk for cancer.
- This cancer risk estimate represents the number of possible excess cancers and not the number of cancers in the community. This numeric estimate is used as a guide for ATSDR recommending public health actions.
- ATSDR suggests that homeowners lower their exposure to carbon tetrachloride in their drinking water by using a different source of drinking water (such as bottled water) or by installing a treatment system that will reduce the amount of carbon tetrachloride in their water.

Case Study Exercise: Conducting the Toxicological Evaluation

In Module 7, you learned about various steps in the health effects evaluation process. You also did a case study exercise on the steps that Module 7 focused on, working with arsenic data for the soil at the daycare center.

In this mini-module, you will use the same case study exercise information (arsenic in soil) but focus only on the toxicological evaluation piece. As you learned, this is the 7th step in the evaluation process covered in Module 7.

Let’s get started.

Case Study Exercise: Overview

Now, you will perform the toxicological evaluation for **arsenic in soil** to closely examine (1) the doses that resulted in HQs and CRs above acceptable levels, and (2) the intermediate doses that had no duration-specific health guideline available to enable a comparison. This table includes the doses you flagged as needing a toxicological evaluation because they resulted in HQs above 1.0 (Step 5) and CRs above 1.0E-6 (Step 6) in Module 7.

Exposure Group	Duration	Estimated Exposure Dose (mg/kg/day)	Arsenic MRL	HQ	Next Step: Non-Cancer	Cancer Risk	Next Step: Cancer
Children 1 to <2 years	Chronic	0.0039	0.0003	13	Toxicological Evaluation	7.5E-5	Toxicological Evaluation
Children 2 to <6 years	Chronic	0.0026	0.0003	8.7	Toxicological Evaluation	2.0E-4	Toxicological Evaluation
Adults	Chronic	0.00028	0.0003	0.93	No Action	1.3E-4	Toxicological Evaluation
Pica children 1 to <2 years	Acute	0.12	0.005	23	Toxicological Evaluation	NC	Not applicable
Pica children 2 to <6 years	Acute	0.075	0.005	15	Toxicological Evaluation	NC	Not applicable
Pica children 1 to <2 years	Intermediate	0.12	Not available	NC	Toxicological Evaluation	NC	Not applicable
Pica children 2 to <6 years	Intermediate	0.075	Not available	NC	Toxicological Evaluation	NC	Not applicable

Exercise: Identify Data from Key Studies

The table presented next is like the one we did together in Section 2. But now, you will use available source information to fill in the missing pieces for the non-cancer health guidelines.

ATSDR has a Toxicological Profile for Arsenic. You will use this source to fill in the missing non-cancer data in the table for the acute MRL and chronic MRL (there is no intermediate MRL for arsenic).

Note that ATSDR also has an Addendum to the Toxicological Profile for Arsenic that includes scientific data published since the profile was released. For simplicity in the training, you will use the Toxicological Profile as your sole source of information here.

After you fill out the table in the next slide, go to the slide after that to check your answers.

Exercise (cont.)

Fill in the empty pieces in the table below. Check your answers on the next slide.

Identify data from key studies for non-cancer effects — arsenic

Parameter	Data for Acute Non-cancer Health Effects	Data for Chronic Non-cancer Health Effects
Health guideline value	Acute MRL: 0.005 mg/kg/day	Chronic MRL: 0.0003 mg/kg/day
Information source	ATSDR Toxicological Profile for Arsenic	ATSDR Toxicological Profile for Arsenic
Study reference for health guideline		
Exposure route and duration evaluated		
No-observed-adverse-effect level (NOAEL), if one was reported (include units)		
Lowest-observed-adverse-effect level (LOAEL), if one was reported (include units)		0.002 mg/kg/day (based on collective studies)
Observed effect		
Species LOAEL/NOAEL/BMDL is based on		
Dosing method and exposure medium	Dietary intake of arsenic-contaminated soy sauce	Ingestion of contaminated drinking water
Uncertainty factors (UF)	10	3

Exercise (cont.2)

How did you do? Look at the completed table here.

Identify data from key studies for non-cancer effects — arsenic

Parameter	Data for Acute Non-cancer Health Effects	Data for Chronic Non-cancer Health Effects
Health guideline value	Acute MRL: 0.005 mg/kg/day	Chronic MRL: 0.0003 mg/kg/day
Information source	ATSDR Toxicological Profile for Arsenic	ATSDR Toxicological Profile for Arsenic
Study reference for health guideline	Mizuta et al. 1956	Tseng 1977; Tseng et al. 1968
Exposure route and duration evaluated	Oral, acute	Oral, chronic
No-observed-adverse-effect level (NOAEL), if one was reported (include units)	NA	0.0008 mg/kg/day
Lowest-observed-adverse-effect level (LOAEL), if one was reported (include units)	0.05 mg/kg/day	0.002 mg/kg/day (based on collective studies)
Observed effect	Dermal and gastrointestinal effects	Dermal effects
Species LOAEL/NOAEL/BMDL is based on	Humans	Humans
Dosing method and exposure medium	Dietary intake of arsenic-contaminated soy sauce	Ingestion of contaminated drinking water
Uncertainty factors (UF)	10	3

NA = not available / not applicable

Case Study Exercise: Review Journal Articles, if Needed

You closely evaluated the Arsenic Toxicological Profile for the health guidelines from ATSDR (acute and chronic MRLs) and put that information into the table.

Based on the information available, we have confidence in these studies used by ATSDR to support the development of these health guidelines. Thus, for this exercise, no action is required for this step.

But at your real sites, if needed and appropriate, do review the original journal articles that were the basis for the health guidelines developed as well any newer studies.

Case Study Exercise: Evaluate the Evidence, Non-Cancer

In Section 2, for *non-cancer* effects, you learned how to calculate a numeric comparison of the health effect study levels and the site doses (also called MOE). An example equation involves dividing the lowest-observed-adverse-effect level (LOAEL) reported in the critical study by the site-specific exposure dose equation as:

LOAEL / site-specific exposure dose

This calculation helps you see how close your site-specific dose is to an observed effect level (such as a LOAEL, BMDL, HED_{LOAEL}). For instance, let's take an example site-specific dose for this case study exercise of 0.0039 mg/kg/day and the LOAEL for arsenic of 0.002 mg/kg/day. The formula for this calculation would be 0.002 / 0.0039 = 0.51. This result shows you that your site-specific dose exceeds the LOAEL.

Case Study Exercise: Evaluate the Evidence, Non-Cancer (cont.)

A MOE *below* 1, like in this example, indicates your site-specific dose is above the health effect study level and will need further examination. A value *above 1* means your site-specific dose is below the health effect study level.

But even in cases where your site-specific dose is below the observed effect level, you will still need to review the toxicological information to determine whether the site-specific dose is close enough to the observed effect level and use professional judgment to conclude if there is or is not a risk of harmful effects.

Case Study Exercise: Evaluate the Evidence, Non-Cancer (cont.2)

When evaluating the toxicological evidence, which is true about evaluating non-cancer effects? Choose all that apply.

__A) Calculate a numeric comparison of health effect study levels and site doses

to assess non-cancer health effects (also called MOE).

__B) An example formula to calculate the MOE is LOAEL / site-specific exposure dose.

__C) Health assessors should use information from the toxicological profile and IRIS, as well as the evaluation of evidence and professional judgement, when deciding whether non-cancer health effects might be possible.

__D) ATSDR has a specific scheme to determine the confidence (such as low, medium, high) in the MRL, the study, or the health endpoints.

After you pick your answer, go to the next slide to check it.

Exercise: Evaluate the Evidence, Non-Cancer (cont.3)

Here's the answer. How did you do?

Answers "A," "B," and "C" are correct. As you learned in Section 2, ATSDR does not has a specific scheme to determine the confidence (such as low, medium, high) in the MRL, the study, or the health endpoints.

Exercise: Evaluate the Evidence, Non-Cancer (cont.4)

Now we need to identify data from the ATSDR Toxicological Profile associated with intermediate soil ingestion, which had no health guidelines available to evaluate non-cancer hazards.

When a health guideline is not available, health assessors should compare the estimated site-specific doses or concentrations for an exposure duration directly to the doses from animal and human studies. Those studies should be based on the same exposure duration to determine whether exposures over that duration could cause harm.

Exercise: Evaluate the Evidence, Non-Cancer (cont.5)

Now you need to identify data from the Toxicological Profile associated with studies on intermediate ingestion, which has no health guideline. Go to Table 3-3. Levels of Significant Exposure to Inorganic Arsenic — Oral in the ATSDR Toxicological Profile.

Based on all the doses shown, which is the lowest intermediate LOAEL reported for humans exposed to inorganic arsenic?

Exercise: Evaluate the Evidence, Non-Cancer (cont.6)

How did you do?

Option “A” is correct. A LOAEL of 0.05 mg/kg/day was reported in a human study by Huang et al. 1985, based on the development of hyperpigmentation with keratosis.

Exercise: Evaluate the Evidence, Cancer

In Section 2, for *cancer* effects, you learned that the approach to evaluate the toxicological evidence includes various components, such as:

- Estimating theoretical increased risk of cancer in an exposed population by multiplying the site-specific exposure dose estimate by an oral CSF or the site-specific air concentration by the IUR.
- Discussing the types of cancer that might be possible and being mindful of cancers that may be route specific.
- Using professional judgment to decide whether cancer effects are possible.

You also learned about steps that ATSDR does not perform during this approach for cancer, including:

- Do not conduct a comparison between the cancer effect level (CEL) and site exposure dose.
- Do not use a CEL to make a health hazard conclusion.

Exercise: Evaluate the Evidence, Cancer (cont.)

Also in Section 2, we talked about examples of information you might collect to examine potential cancer effects. This information is found in the ATSDR Toxicological Profile, EPA IRIS, and ATSDR Health Guidelines and Cancer Risk Table (for the cancer classifications). For this arsenic exercise, we put the cancer effects information into the table below for you.

Identify data from key studies and other information cancer effects — arsenic

Parameter	Data for Cancer Effects
Cancer risk value	CSF: 1.5 mg/kg/day^{-1}
Information source for cancer risk value	EPA IRIS
Study reference	Tseng 1977; Tseng et al. 1968
Study exposure route and duration evaluated	Oral, chronic
Observed effect for cancer risk value	Skin cancer
Species cancer risk value is based on	Humans
Dosing method and exposure medium in study	Ingestion of contaminated drinking water
Cancer classifications	A-human carcinogen (EPA), 1-known human carcinogen (NTP), 1-carcinogenic to humans (sufficient human evidence), and OC-occupational carcinogen (NIOSH)

Exercise: Evaluate the Evidence, Cancer (cont.2)

When evaluating the toxicological evidence, which is true about evaluating *cancer effects*? Choose all that apply.

__A) Do not calculate a comparison between the cancer effect level (CEL) and site dose to assess cancer effects.

__B) Use a CEL to make a public health hazard conclusion.

__C) Use the oral cancer slope factor (CSF) or inhalation unit risk (IUR) to calculate the cancer risk (CR) and discuss the types of cancer and routes of exposure to interpret the results.

After you pick your answer, go to the next slide to check it.

Exercise: Evaluate the Evidence, Cancer (cont.3)

Here's the answer. How did you do?

Answers "A" and "C" are correct. As you learned in Section 2, it is not appropriate to use a CEL to make a public health hazard conclusion.

Case Study Exercise: Review Other Health Effects for Similar Doses

At this point in the toxicological evaluation, you will look for doses similar to your site-specific doses that were reported in studies for other health effects (target organs and systems). To help with this step, the table below includes a summary of your doses, the health effects/organ systems for the health guidelines and cancer risk values you used, and whether the next step includes a toxicological evaluation. This information will help you answer the next question.

Exposure Group	Duration	Estimated Exposure Dose (mg/kg/day)	Health Effects for Non-Cancer Health Guideline	Next Step: Non-Cancer	Health Effects for Cancer Risk Value	Next Step: Cancer
Children 1 to <2 years	Chronic	0.0039	Dermal effects	Toxicological Evaluation	Skin cancer	Toxicological Evaluation
Children 2 to <6 years	Chronic	0.0026	Dermal effects	Toxicological Evaluation	Skin cancer	Toxicological Evaluation
Adults	Chronic	0.00028	Dermal effects	No Action	Skin cancer	Toxicological Evaluation
Pica children 1 to <2 years	Acute	0.12	Dermal and gastrointestinal effects	Toxicological Evaluation	Not applicable for acute	Not applicable
Pica children 2 to <6 years	Acute	0.075	Dermal and gastrointestinal effects	Toxicological Evaluation	Not applicable for acute	Not applicable
Pica children 1 to <2 years	Intermediate	0.12	No health guideline	Toxicological Evaluation	Not applicable for intermediate	Not applicable
Pica children 2 to <6 years	Intermediate	0.075	No health guideline	No HG; Toxicological Evaluation	Not applicable for intermediate	Not applicable

Case Study Exercise: Review Other Health Effects for Similar Doses (cont.)

Go to Table 3-3. Levels of Significant Exposure to Inorganic Arsenic — Oral in the ATSDR Toxicological Profile to see doses from studies with other health effects for similar doses to yours. Based on your **chronic doses for children 2 to <6 years** (last page), what other health effect with similar doses might you look at? Choose one answer.

__A) 19 mg/kg/day that caused lethargy

__B) 6 mg/kg/day that caused uncontrolled head shaking

__C) 0.003 mg/kg/day that caused decreased scores in performance on intelligence tests

__D) 93 mg/kg/day that caused encephalopathy

After you pick your answer, go to the next slide to check it.

Case Study Exercise: Review Other Health Effects for Similar Doses (cont.2)

Did you get the right answer?

Option “C” is correct. The dose of 0.003 mg/kg/day is the closest to the doses for your site-specific chronic scenario for children ages 2 to <6 years.

The other doses in answers “A,” “B,” and “D” are all several times higher than your doses and would not be considered comparable.

Case Study Exercise: Review Other Health Effects for Similar Doses (cont.3)

In Section 2 you learned how to compare your site-specific doses to those from studies on the LSE tables and figures in the Toxicological Profile. This is a simple step that gives you perspective on where your site-specific doses fall in relation to those published in scientific studies.

For this exercise, you will examine Table 3-3. Levels of Significant Exposure to Inorganic Arsenic — Oral in the ATSDR Toxicological Profile, but this time you will use the section on acute oral ingestion.

See where your two site-specific acute doses fall on the table. As a reminder, your acute doses are:

- 0.12 mg/kg/day for pica children 1 to <2 years
- 0.075 mg/kg/day for pica children 2 to <6 years

Case Study Exercise: Review Other Health Effects for Similar Doses (cont.4)

Based on comparing your site-specific acute pica ingestion doses to those from scientific studies shown on the LSE table, which statements are true? Choose all that apply.

__A) Both site-specific doses are two times less than the lowest reported dose.

__B) Both site-specific doses are higher than the lowest reported dose.

__C) The site-specific dose for children 1 to <2 years is higher than the lowest reported dose.

__D) The site-specific dose for children 2 to <6 years is lower than the lowest reported dose.

Case Study Exercise: Review Other Health Effects for Similar Doses (cont.5)

Well, did you choose the right answers?

Option “B” is correct. The lowest reported dose presented on the LSE table is 0.05 mg/kg/day. The acute dose for children ages 1 to <2 years of 0.12 mg/kg/day is higher than 0.05 mg/kg/day. The acute dose for children ages 2 to <6 years of 0.075 mg/kg/day is also higher than 0.05 mg/kg/day.

Exercise: Review Contaminant-specific Toxicological Info

As you recall from Section 2, you need to consider various types of information:

- Toxicokinetics (absorption, distribution, elimination, metabolism)
- Mechanisms of action
- Children's susceptibility, including mutagenicity
- Populations that are unusually susceptible
- Interactions with other contaminants
- General population and populations with more than average exposure

You will look through the Toxicological Profile and answer the question on the next page.

Exercise: Review Contaminant-specific Toxicological Info (cont.)

Based on your review of the Toxicological Profile, select all the information about arsenic that might influence a decision about whether harmful effects are possible?

__A) There is no evidence for differences in absorption of arsenic in children and adults.

__B) Arsenic is known to be present in breastmilk at low concentrations.

__C) A study suggested a greater-than-additive interaction between smoking and arsenic exposure.

__D) The toxic effects of chronic arsenic ingestion may be increased in populations that are also subject to malnutrition.

__E) Researchers have found that selenium can decrease the effects of arsenic.

After you choose your answer, go to the next slide to check it.

Exercise: Review Contaminant-specific Toxicological Info (cont.2)

How did you do?

Did you check all of them? Because if you did, you are correct. Answers “A”, “B”, “C”, “D”, and “E” are all pieces of information about arsenic that might influence a decision about whether harmful effects are possible.

Exercise: Consult with a Team Toxicologist or Epidemiologist

Based on your site-specific scenario, what would you want to ask a toxicologist about because of a missing health guideline? Choose the one appropriate answer.

__A) Dose-response data for arsenic ingestion exposures for an intermediate duration.

__B) Dose-response data for arsenic ingestion exposures for an acute duration.

After you choose your answer, go to the next slide to check it.

Exercise: Consult with a Team Toxicologist or Epidemiologist (cont.)

Now, check your answer to see how you did.

Answer “A” is correct because there is no health guideline for intermediate exposure to arsenic.

Answer “B” is incorrect because there is a health guideline for acute exposure to arsenic.

End of Mini-Module: Toxicological Evaluation

Congratulations! You finished this mini-module.

Now, remember that you will need this information to complete the entire health effects evaluation process in Module 7.

For more information, contact ATSDR
1-800-CDC-INFO (232-4636)
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