Mixtures Similarity Tool (MiST)

03/16/2022

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Public Science Meeting on PCB Mixture Assessment Methods

- **Introduction to EPA's human health risk assessment practices for chemical mixtures**
  - *Glenn Rice, U.S. EPA*
- **Mixtures modeling – methods considered for the assessment of polychlorinated biphenyls**
  - *Jeff Gift and Laura Carlson, U.S. EPA*
- **Methods for estimating relative potency values**
  - *Grace Patlewicz, U.S. EPA*
- **Overview of the Mixtures Similarity Tool (MiST)**
  - *Graham Glen and Joanne Trgovcich, ICF*

Introduction to MiST

- Overview of MiST Tool
- Assumptions Built into MiST for Analyses of PCBs Mixtures
- Key Information Needed to Analyze Mixture Similarities
- Demonstration: Sufficient Similarity Evaluation of 4 Aroclor Mixtures with Neurotoxicity Data to Mixtures Similarity Testing Results

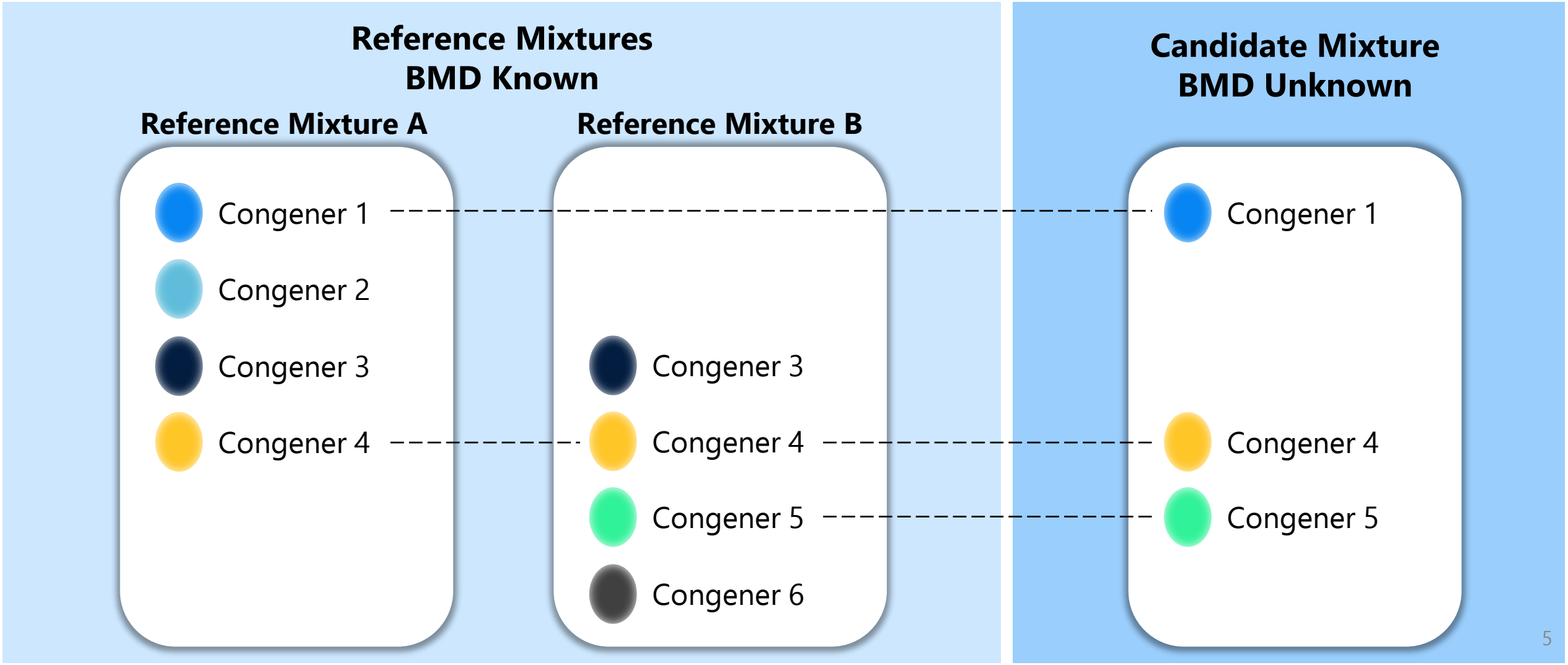
- MiST was developed to support risk assessment of chemical mixtures relevant to human health.

- It is a Microsoft Excel®-based tool for researchers and risk assessors to ascertain the degree to which “candidate mixtures” and “reference mixtures” are similar from a toxicity standpoint.

Mixtures Similarity Tool (MiST)

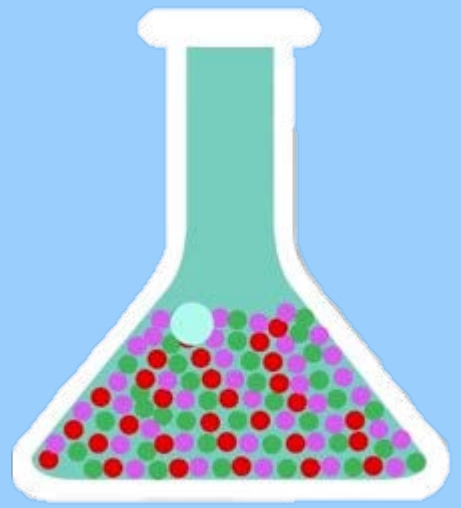
Fundamental Question:

Is the candidate mixture sufficiently similar to any of the reference mixtures such that the reference could be used as a toxicity surrogate?



MiST Compares Candidate and Reference Mixtures

- Reference mixtures are those for which estimated effect levels (e.g., benchmark doses (BMDs)), along with variance information for these estimates, can be or have been derived.
- Candidate mixtures are those selected for risk evaluation that will be compared with a reference mixture to determine sufficient similarity; a candidate mixture might lack adequate dose-response data for deriving estimated effect levels (e.g., many environmental mixtures).



MiST Compares Similarity of One Candidate Mixture to One or More Reference Mixtures

The method is intended to answer two questions:

- Is a given reference mixture "sufficiently similar" to the candidate mixture such that the reference mixture could be used as a toxicological surrogate?
- If more than one reference mixture is "sufficiently similar" to the candidate mixture, which reference mixture is the most appropriate toxicological surrogate?

MiST Methodology

MiST implements a modified method published by Gennings and colleagues:

Marshall, S., Gennings, C., Teuschler, L. K., Stork, L. G., Tornero-Velez, R., Crofton, K. M., & Rice, G. E. (2013). An empirical approach to sufficient similarity: Combining exposure data and mixtures toxicology data. Risk Analysis, 33(9), 1582-1595.

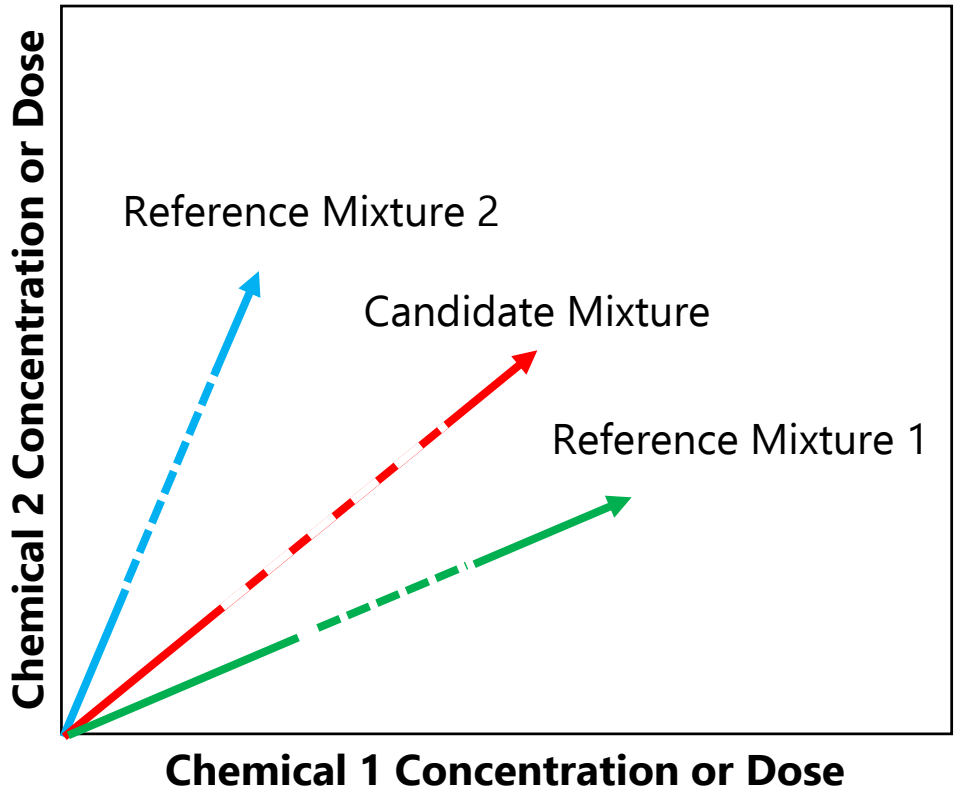
MiST Modifications to the Marshall et al. Method:

1. Use of the Monte-Carlo method to estimate the distribution of distances between the reference and candidate mixture BMDs. The advantage is that the Monte Carlo approach does not rely on the BMD estimates being normally distributed.
2. The amended method considers one candidate mixture and one or multiple reference mixture(s).

MiST Calculates the Average Euclidean Distance Between Reference and Candidate Mixtures

- **The critical value** for each reference is typically set to the absolute value of the difference between the effective dose (ED) and median BMD value.
- If the upper 95th percentile of the "distance" (D_wU_{95}) is less than the critical value (Δ), then the reference is "sufficiently similar" to the candidate
- If several reference mixtures are compared to the same candidate mixture, the reference mixture with the smallest mean distance is distinguished as the best match to the candidate mixture

Derivation of DwU_{95} Using MC Approach

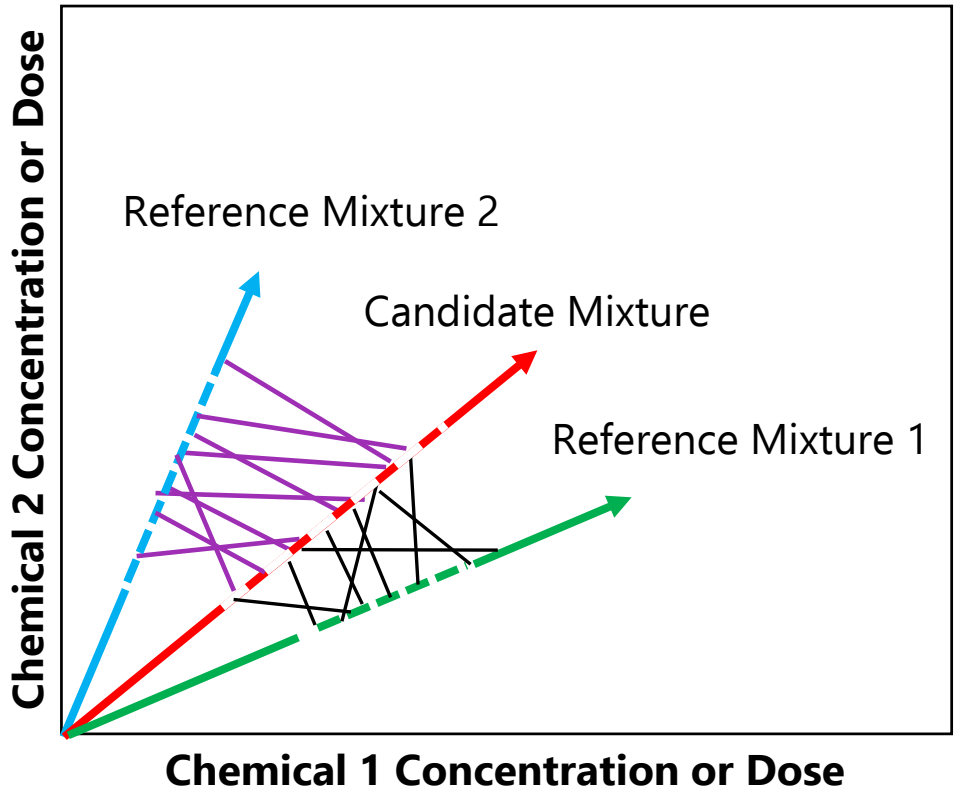


A mixture's BMD is a point on its mixture composition vector (blue, red and green lines).

This example depicts simple mixtures of two chemicals for ease of illustration, but the same principles apply for PCB mixtures of up to 209 congeners.

- Length of dashed portion of lines reflect the uncertainty distributions of their BMDs.

Derivation of DwU_{95} Using MC Approach



Distance between reference 1 BMD and candidate BMD

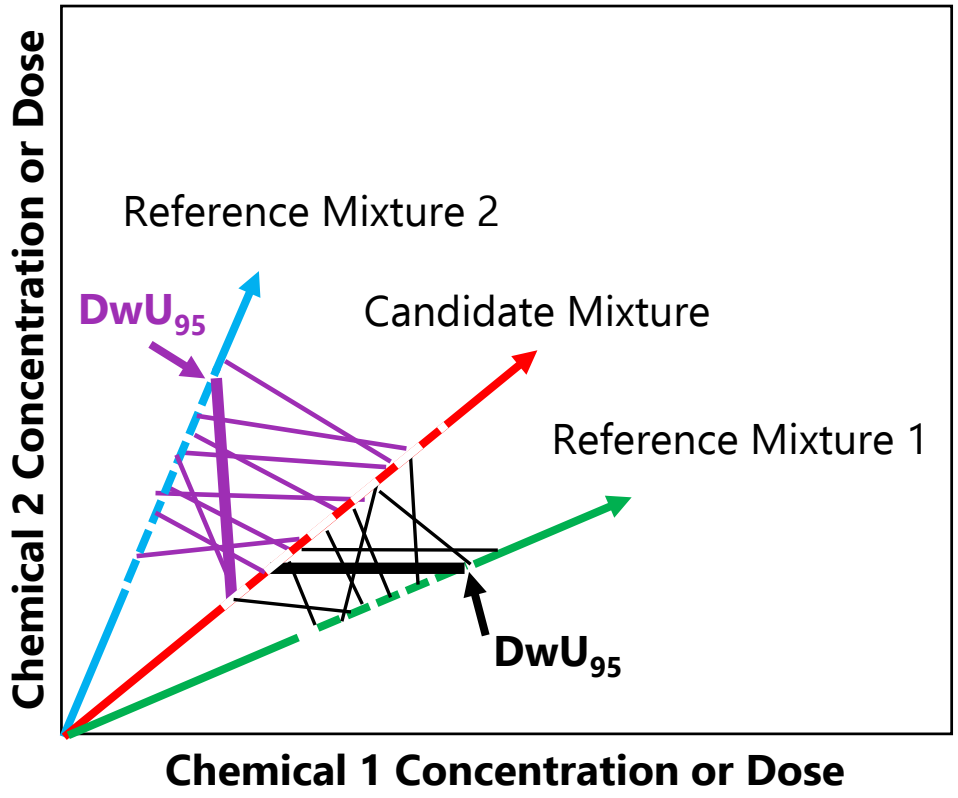
Distance between reference 2 BMD and candidate BMD

A mixture's BMD is a point on its mixture composition vector (blue, red and green lines).

This example depicts simple mixtures of two chemicals for ease of illustration, but the same principles apply for PCB mixtures of up to 209 congeners.

- Length of dashed portion of lines reflect the uncertainty distributions of their BMDs.
- Thousands of Monte Carlo iterations are performed to estimate distances (D_w) between candidate BMD and the BMDs for reference 1 (black lines) and reference 2 (purple lines).

Derivation of DwU_{95} Using MC Approach



Distance between reference 1 BMD and candidate BMD

Distance between reference 2 BMD and candidate BMD

A mixture's BMD is a point on its mixture composition vector (blue, red and green lines).

This example depicts simple mixtures of two chemicals for ease of illustration, but the same principles apply for PCB mixtures of up to 209 congeners.

- Length of dashed portion of lines reflect the uncertainty distributions of their BMDs.
- Thousands of Monte Carlo iterations are performed to estimate distances (D_w) between candidate BMD and the BMDs for reference 1 (black lines) and reference 2 (purple lines).
- Mixtures are considered similar if the distances between the candidate and references are less than the critical value for at least 95% of Monte Carlo iterations (DwU_{95} (bold lines) < Δ) .

General Assumptions Built into MiST

1. The chemical mixtures consist of 209 components
   - There are no other chemicals in the mixture
   - The congener mass fractions sum to one
2. The health effects for all reference mixtures and any candidate mixtures in a single analysis are comparable
3. The difference between the candidate and reference BMDs (calculated as the weighted Euclidean distance between them) defines how toxicologically “similar” the two mixtures are to each other

BMD Assumptions Built into MiST

1. Each reference mixture has a BMD, or BMD-like estimate, with an associated uncertainty distribution, for the health effect of interest for the analysis
    - The BMD of a mixture is the weighted sum of the BMD of its congeners
    - There is no synergism or antagonism among congeners (dose additivity)
2. The BMD distribution for the candidate mixture is independent of those for the reference mixtures, meaning the covariance between the two distributions is assumed to be zero

PCB Mixture Assumptions Built into MiST

1. The congener mass fractions sum to 1 and are specified without any estimate of their potential uncertainty or error
2. The relative potency of each congener is specified without an estimate of uncertainty or error
3. The “relative toxicological potencies” of all congeners in a mixture should sum to 209

Key Mixture Information for MiST

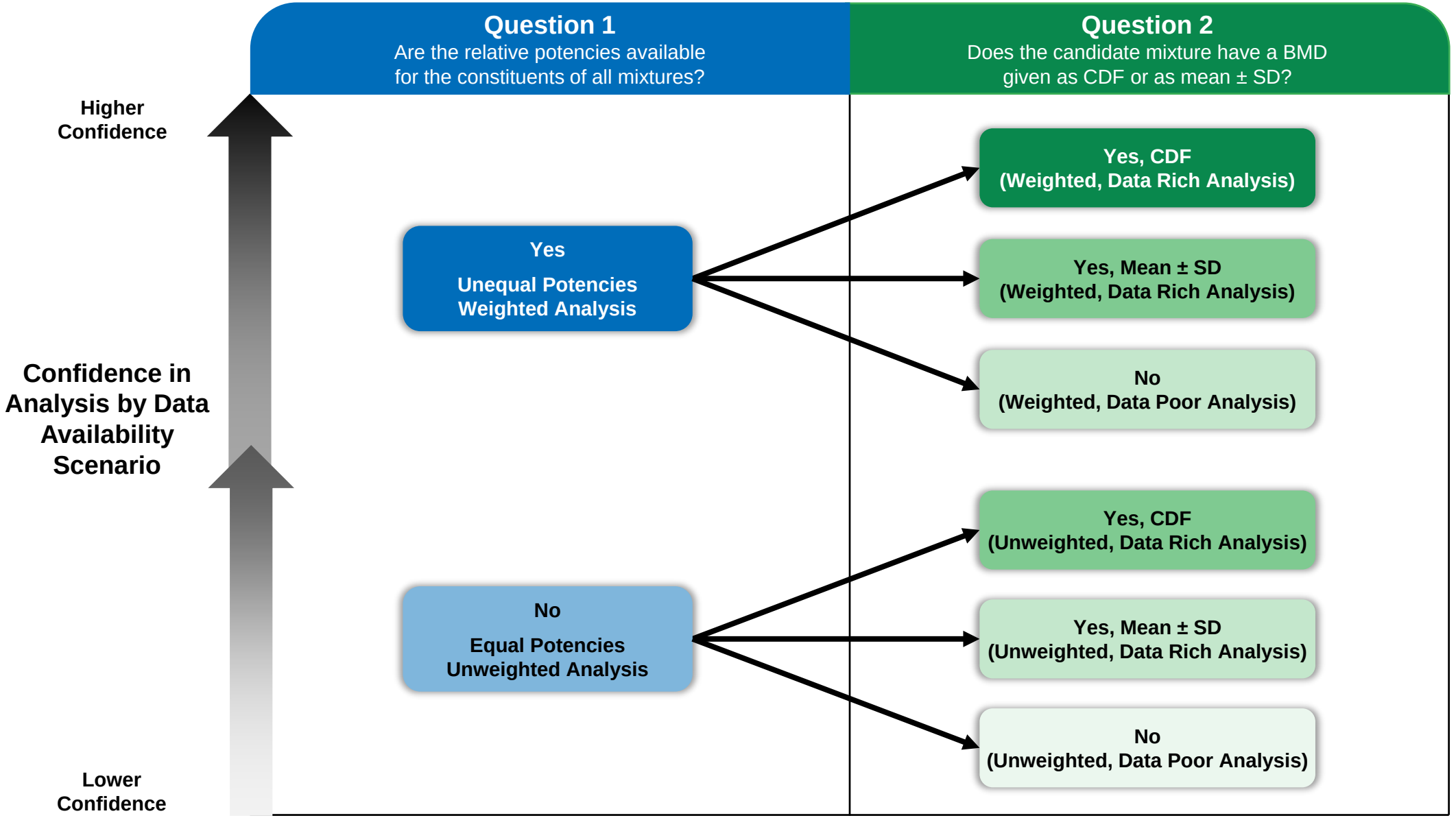
- Mass fraction of each congener in the candidate and reference mixtures
- BMD ± SD or BMD Cumulative Distribution Function (CDF) for each reference mixture
- Effective dose (ED) for each reference mixture

Key Questions Define the Mixture Analysis Options

Are relative potencies available for the congener constituents of the mixture?

Does the candidate mixture have BMD information?

Visual Depiction of Key Questions that Frame Data Availability Scenarios in MiST



MiST: A Microsoft EXCEL based tool

Required information:

1. Mass fraction of each congener in the candidate and reference mixtures
2. BMD ± SD or BMD Cumulative Distribution Function (CDF) for the reference mixture
3. Effective dose (ED) for reference mixture (used to calculate the critical value (i.e., Δ))

Optional Data:

1. BMD ± SD or CDF for the candidate mixture
2. The relative toxicity of different constituents in the mixtures

MiST Demo: Sufficient Similarity Evaluation of 4 Aroclor Mixtures with Neurotoxicity Data

- BMD modeling for a neurological endpoint (landing foot splay). Data from Freeman et al. An assessment of neurotoxicity of Aroclors 1016, 1242, 1254, and 1260 administered in diet to Sprague-Dawley rats for one year. Toxicol Sci. 2000 Feb;53(2):377-91. PMID: 10696786.
- Calculated BMD and CDF
- Used congener toxicological potency values for neurotoxicity from Pradeep et al. (2019) *Regul Toxicol Pharmacol*. 101:12-23
- Used congener mass fraction data from ATSDR TOXICOLOGICAL PROFILE FOR POLYCHLORINATED BIPHENYLS (PCBs), November 2000.
- Assessed similarity between a candidate mixture (Aroclor 1254) and three reference mixtures (Aroclors 1016, 1242, and 1260)

Opening the Tool

MiST

Mixtures Similarity Tool

Version 1.1
Version Date: 2/18/2022

SECURITY WARNING Macros have been disabled. Enable Content

Background

MiST (Mixtures Similarity Tool) implements a mixtures similarity approach from Marshall
Marshall, S., Gennings, C., Teuschler, L. K., Stork, L. G., Tornero-Velez, R., Crofton, K. M., &
data. Risk Analysis, 33(9), 1582-1595.

This method is amended to allow for Monte-Carlo evaluation of the **benchmark dose (BMD)** ar
variance information (e.g., a standard deviation [SD]). **BMDs** and **extra risk concentrations**
refer to any type of adverse effect level compatible with the tool.
A detailed description of the theoretical framework and methodology is provided in the
Highlighted terms and abbreviations in this tab and the Quick Start Guide tab are also defined a

The amended method compares one "candidate mixture" and one or more "reference m
1) Is a given reference mixture "**sufficiently similar**" to the candidate mixture such
2) If more than one reference mixture is "sufficiently similar" to the candidate mixtu

To support these conclusions, the method establishes the "distance" between two mixt
1) **Mass fraction** for each PCB congener in the mixture (required for all mixtures)
2) Estimated dose associated with an adverse effect level (e.g., BMD or ERCs from EPA's **CatReg** software)
*Please consult the EPA **BMDS** Technical Guidance (EPA/630/R-00/001) or the CatReg software User Manual (EPA/600/R-17/236)*
3) (optional) The toxicological potency of each PCB congener relative to the potency of the same congener (often, the most toxic congener);
Note: For PCBs, the **relative toxicological potencies** vary by health effect.

MiST

Mixtures Similarity Tool

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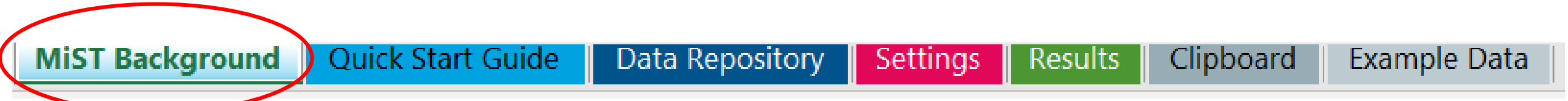
MiST Background Tab



The MiST Background provides general information about the method MiST uses to answer 2 questions informing toxicological similarity of PCB mixtures:

1. Is a given reference mixture "sufficiently similar" to the candidate mixture such that the reference mixture could be used as a toxicity surrogate?

2. If more than one reference mixture is "sufficiently similar" to the candidate mixture, which reference mixture is the best match to the candidate mixture?

A comprehensive description of MiST methodology, assumptions, and validation tests are provided in the User Guide

QuickStart Guide

The Quick Start Guide offers a condensed set of instructions for using MiST

A comprehensive set of instructions is available in the User Guide

MiST
Mixtures Similarity Tool

Version 1.1
Version Date: 2/18/2022

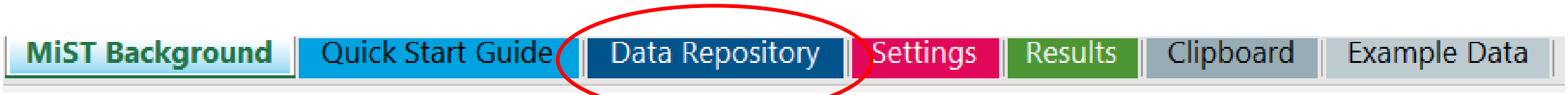
Getting Started:

1. Detailed instructions are provided in the MiST User Guide.
2. Users are encouraged to save an original version of MiST before beginning their analyses. Saving an unused version of MiST ensures access to a backup copy if the user inadvertently deletes or disrupts codes hidden in
3. Users without administrative privileges may encounter difficulty enabling macros. MiST also includes a hidden Templates tab that defines data validated terms used in MiST. Users unable to enable macros or who wish to view the templates should consult with their employer's IT professionals to modify these settings. Users with administrative control can find additional guidance through Microsoft Excel support.
4. Macros running other excel files may interfere with macros coded in MiST. Therefore, users should close any other macro-enabled excel file prior to opening MiST.

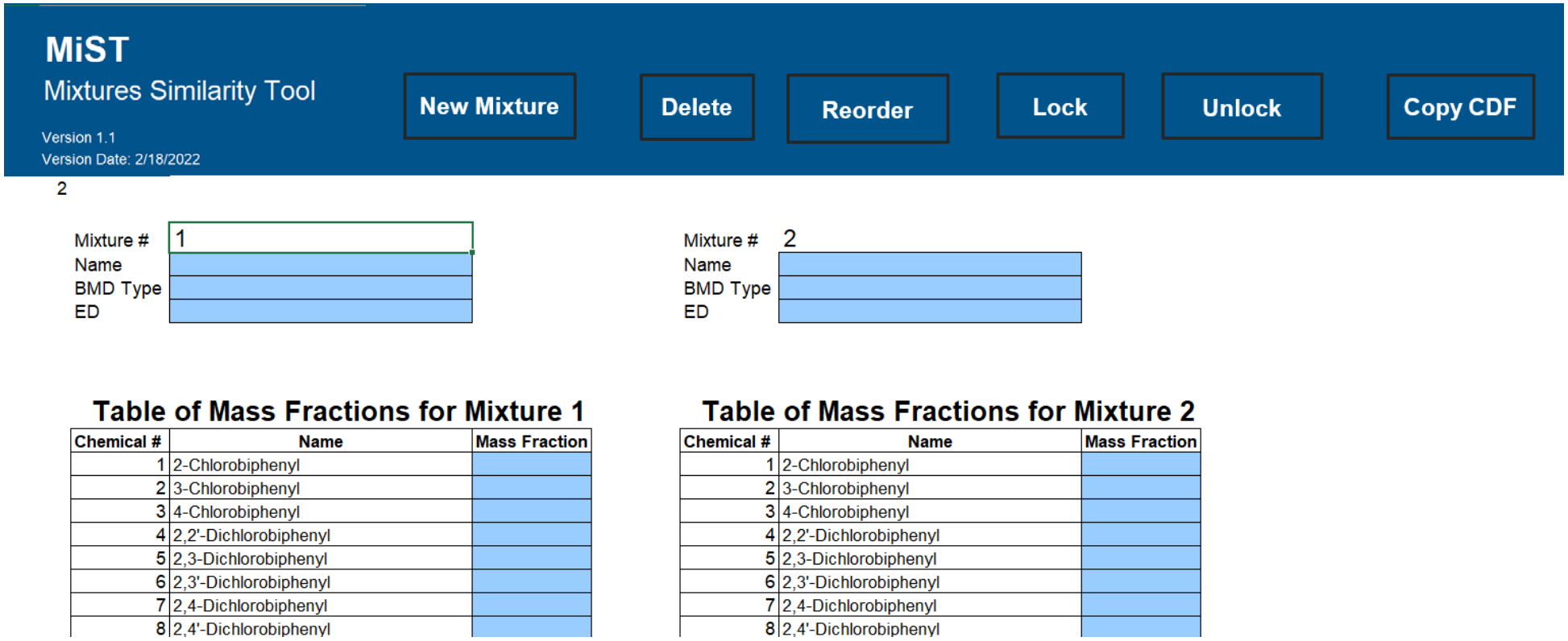
Running MiST involves selecting the appropriate data scenario and entering inputs for the candidate mixture and reference mixture(s).

Tab name	Step	Action	Details
Quick Start Guide	Setup	Make sure that macros are enabled in Excel.	Either click the "Enable Content" button at the top when opening Excel or: 1. Click the File tab 2. Click Options 3. Click Trust Center 4. Click Trust Center Settings 5. Click Macro Settings 6. Select "Enable all macros"
Data Repository	Step 1: Enter Mixture Properties	1. Select a mixture to edit by clicking the "Unlock" button.	*Note* : When prompted "Unlock Which Mix?", enter the mixture number. Cells will turn blue when unlocked. *Note:* When entering a series of new mixtures, users should select the button to add new mixture (s) for the intended analyses prior to entering data in the 'Setitngs Tab'. Once new mixtures are entered, users can select mixtures to edit/enter mixture properties.
		2. Enter the name of the mixture.	Mixture # populates automatically *Note* : The name will be used in the in the 'Settings' tab to run the analysis.
		3. Select one of three BMD types: a. CDF b. Mean & SD c. None	After selecting the BMD type, the tool will direct the user to input either the CDF or Mean & SD for the mixture, below the list of mass fractions. *Note:* When copying and pasting data, users should select the top cell where data will be pasted before copying and pasting data into that cell

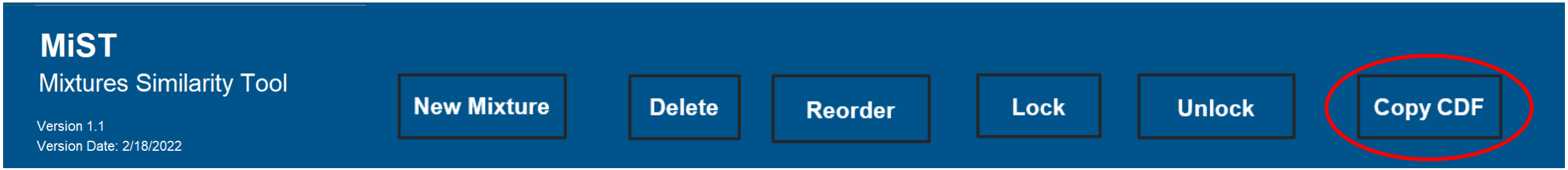
Data Repository Tab



The Data Repository Tab is set up for users to input mixture information including BMD information and mass fraction data

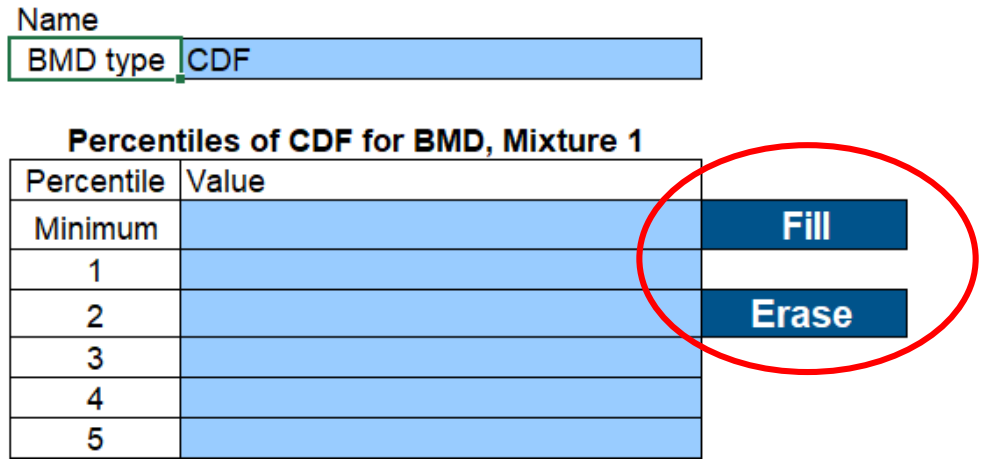


Entering CDF Information



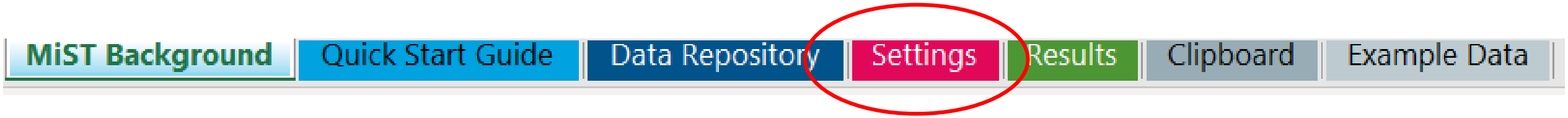
- If CDF values are entered into the clipboard, they can be automatically copied into the Data Repository Tab using the “Copy CDF” button
- The BMD value should be entered as a whole number or decimal greater than zero in non-decreasing order.
- If a user does not have BMD values for every percentile, a piecewise linear interpolation function can be performed to estimate the values for the missing percentiles of the CDF using “Fill” button.

Using "Fill" Buttons to Interpolate Missing CDF Values



1. All 101 values are specified. These are the minimum, percentiles 1-99, and the maximum.
2. BMD values can be entered for CDF percentiles as whole numbers or decimals
3. No value may be negative
4. No value may be smaller than a value at a lower percentile.
5. If two or more values are entered, the user may use the "Fill" button to populate the rest.
   - Each integer percentile gap (between two specified values) is filled by linear interpolation.
   - Interpolation can be used to fill towards the minimum value, the maximum value, or in both directions.
   - Values above the highest specified percentile are filled using the same slope (increase per percentile) as occurs between the two largest specified values. The same logic applies to interpolation to the minimum.

The Settings Tab



The user should fill in key information regarding the run type on the settings tab

Here the user also inputs congener potency estimates, if available

The analysis is also initiated, saved, or edited in the Settings tab

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Mixtures Similarity Tool

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Edit | New Run | Save | Run Analysis

Step 1: Fill in mixture properties on the Data Repository sheet, and Lock
Step 2: Select potencies and (optionally) the critical value
Step 3: Select data rich or data poor method
Step 4: Select one locked candidate mixture, and one or more locked reference mixtures
Step 5: Run analysis and view results

Reference Mixtures

Use equal or unequal potencies?	
Critical value (optiona)	
Data rich or data poor	
Candidate mixture name:	
Number of Reference Mixtures:	

Chemical #	Name	Relative Potencies	Equal Potency
1	2-Chlorobiphenyl		1
2	3-Chlorobiphenyl		1
3	4-Chlorobiphenyl		1
4	2,2'-Dichlorobiphenyl		1
5	2,3-Dichlorobiphenyl		1
6	2,3'-Dichlorobiphenyl		1

The Results Tab

The Results Tab provides the user with the Run Settings, and the results of the similarity analyses

Run Settings

Use equal or unequal potencies?	Unequal
Critical value (optional)	
Data rich or data poor	Data rich
Candidate mixture name:	AR1254
Number of Reference Mixtures:	3

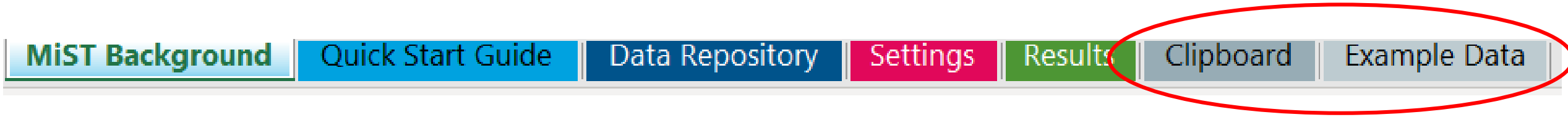
Candidate Mixture	**AR 1254**
BMD	25.855
ED	77.56
Nearest Reference	AR 1242
Distance Dw (mean)	14.659

Reference Mixture	**AR 1242**
BMD	34.564
ED	103.69
Delta	69.126
Dw (Mean)	14.659
Dw (Upper 95th)	58.298
Conclusion	Acceptable
Rank	1

Reference Mixture	**AR 1260**
BMD	19.364
ED	58.09
Delta	51.705
Dw (Mean)	40.381
Dw (Upper 95th)	310.392
Conclusion	Not Acceptable
Rank	2

Reference Mixture	**AR 1016**
BMD	110.38
ED	331.14
Delta	220.76
Dw (Mean)	3582.754
Dw (Upper 95th)	34458.203
Conclusion	Not Acceptable
Rank	3

The Clipboard and Example Data Tabs



The Clipboard Tab

- User may enter CDF data here
- Enables user to copy or enter data from various sources (e.g., EPA BMDS software output, data from published manuscripts, etc.)
- Provides a space for users to review and perform QC on CDF values
- Entering data into the clipboard first ensures all values are in an acceptable format for pasting into the Data Repository and Settings tabs

The Example Data Tab

- Includes data for users to practice entering data for each tab

Demonstration

MiST
Mixtures Similarity Tool

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New Mixture | Delete | Reorder | Lock | Unlock | Copy CDF

2

Mixture #	1
Name	AR 1254
BMD Type	CDF
ED	77.56

Mixture #	2
Name	
BMD Type	
ED	

Table of Mass Fractions for Mixture 1

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0
2	3-Chlorobiphenyl	0
3	4-Chlorobiphenyl	0
4	2,2'-Dichlorobiphenyl	0
5	2,3-Dichlorobiphenyl	0

Table of Mass Fractions for Mixture 2

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0
2	3-Chlorobiphenyl	0
3	4-Chlorobiphenyl	0
4	2,2'-Dichlorobiphenyl	0
5	2,3-Dichlorobiphenyl	0

Mixture #	1
Name	AR 1254
BMD Type	CDF
ED	77.56

Navigate to Data Repository tab, then:

1. Enter mixture name
2. Enter ED
3. Select BMD type

Demonstration

4. Enter mean and SD or CDF values
   - Selecting BMD type moves cursor to cells below mass fraction table

205	2,3,3',4,4',5,5',6-Octachlorobiphenyl	0
206	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl	0
207	2,2',3,3',4,4',5,6,6'-Nonachlorobiphenyl	0
208	2,2',3,3',4,5,5',6,6'-Nonachlorobiphenyl	0
209	Decachlorobiphenyl	0

Name AR 1254
BMD type CDF

Percentiles of CDF for BMD, Mixture 1

Percentile	Value
Minimum	
1	
2	
3	
4	
5	

Fill
Erase

205	2,3,3',4,4',5,5',6-Octachlorobiphenyl	0
206	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl	0
207	2,2',3,3',4,4',5,6,6'-Nonachlorobiphenyl	0
208	2,2',3,3',4,5,5',6,6'-Nonachlorobiphenyl	0
209	Decachlorobiphenyl	0

Name AR1242
BMD type Mean & SD

Normal Distribution Parameters for BMD, Mixture 2

Mean	118.5
Std. Dev.	11.61

Demonstration

Mixture #	1
Name	AR 1254
BMD Type	CDF
ED	77.56

5. Enter Mass Fraction Data

Congener mass fractions are defined as mass of the congener divided by total mass of all congeners in the mixture

$$W_i = (m_i/m_T)$$

W_i =mass fraction of the i^{th} congener
m_i = mass of the i^{th} congener
mT (mass of all congeners) =m1+m2+m3+…

MiST automatically calculates W_i given user-inputted m_i values

Table of Mass Fractions for Mixture 1

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0
2	3-Chlorobiphenyl	0
3	4-Chlorobiphenyl	0
4	2,2'-Dichlorobiphenyl	0.00060084
5	2,3-Dichlorobiphenyl	0
6	2,3'-Dichlorobiphenyl	0.00020028
7	2,4-Dichlorobiphenyl	0
8	2,4'-Dichlorobiphenyl	0.00130182
9	2,5-Dichlorobiphenyl	0
10	2,6-Dichlorobiphenyl	0
11	3,3'-Dichlorobiphenyl	0
12	3,4-Dichlorobiphenyl	0
13	3,4'-Dichlorobiphenyl	0
14	3,5-Dichlorobiphenyl	0
15	4,4'-Dichlorobiphenyl	0.00030042
16	2,2',3-Trichlorobiphenyl	0.00090126
17	2,2',4-Trichlorobiphenyl	0.00090126
18	2,2',5-Trichlorobiphenyl	0.0025035
19	2,2',6-Trichlorobiphenyl	0
20	2,3,3'-Trichlorobiphenyl	0

Demonstration

6. Lock the mixture

Repeat steps 1-6 for each Mixture in the Analysis

1. Enter Mixture Name
2. Enter ED
3. Select BMD type
4. Enter mean and SD or CDF values
5. Enter Mass Fraction values
6. Lock the mixture

- Blue cells can be edited
- Cells appear white when mixtures are locked

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Mixtures Similarity Tool

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New Mixture | Delete | Reorder | Lock | Unlock | Copy CDF

4

Mixture #	1
Name	AR 1254
BMD Type	CDF
ED	77.56

Mixture #	2
Name	AR 1242
BMD Type	CDF
ED	103.69

Mixture #	3
Name	AR 1260
BMD Type	CDF
ED	58.09

Mixture #	4
Name	AR 1016
BMD Type	CDF
ED	331.14

Table of Mass Fractions for Mixture 1

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0
2	3-Chlorobiphenyl	0
3	4-Chlorobiphenyl	0
4	2,2'-Dichlorobiphenyl	0.000600841
5	2,3-Dichlorobiphenyl	0

Table of Mass Fractions for Mixture 2

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0.005385459
2	3-Chlorobiphenyl	0.000299192
3	4-Chlorobiphenyl	0.001795153
4	2,2'-Dichlorobiphenyl	0.030717064
5	2,3-Dichlorobiphenyl	0.00139623

Table of Mass Fractions for Mixture 3

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0.000200797
2	3-Chlorobiphenyl	0
3	4-Chlorobiphenyl	0
4	2,2'-Dichlorobiphenyl	0.000200797
5	2,3-Dichlorobiphenyl	0

Table of Mass Fractions for Mixture 4

Chemical #	Name	Mass Fraction
1	2-Chlorobiphenyl	0.005197921
2	3-Chlorobiphenyl	0.00019992
3	4-Chlorobiphenyl	0.0014994
4	2,2'-Dichlorobiphenyl	0.036185526
5	2,3-Dichlorobiphenyl	0.00169932

Demonstration

Navigate to the Settings tab, then:

7. Choose Equal or Unequal Potencies
8. Choose data availability scenario (data rich or data poor)
9. Identify the candidate mixture
10. Identify the reference mixture(s)

MiST
Mixtures Similarity Tool
Version: 11/19/2021

Edit | New Run | Save | Run Analysis

Step 1: Fill in mixture properties on the Data Repository sheet, and Lock
Step 2: Select potencies and (optionally) the critical value
Step 3: Select data rich or data poor method
Step 4: Select one locked candidate mixture, and one or more locked reference mixtures
Step 5: Run analysis and view results

Use equal or unequal potencies?	Unequal
Critical value (optiona)	
Data rich or data poor	Data rich
Candidate mixture name:	AR1254
Number of Reference Mixtures:	3

Reference Mixtures
AR1242
AR1016
AR1260

Chemical #	Name	Relative Potencies	Equal Potency
1	2-Chlorobiphenyl	0.352	1
2	3-Chlorobiphenyl	0.209	1
3	4-Chlorobiphenyl	0.222	1

If congener potencies are unknown, MiST assumes equal potencies

Demonstration

11. After reviewing inputs, Run the Analysis

- Users may also Edit the inputs, Save the analysis, or set up a New Run on the Settings Tab
- When saving an analysis, save under a new filename to avoid overwriting the original MiST file

MiST
Mixtures Similarity Tool

Version 1.1
Version Date: 2/18/2022

Edit | New Run | Save | Run Analysis

Step 1: Fill in mixture properties on the Data Repository sheet, and Lock
Step 2: Select potencies and (optionally) the critical value
Step 3: Select data rich or data poor method
Step 4: Select one locked candidate mixture, and one or more locked reference mixtures
Step 5: Run analysis and view results

Use equal or unequal potencies?	Unequal
Critical value (optional)	
Data rich or data poor	Data rich
Candidate mixture name:	AR 1254
Number of Reference Mixtures:	3

Reference Mixtures
AR 1242
AR 1260
AR 1016

Chemical #	Name	Relative Potencies	Equal Potency
1	2-Chlorobiphenyl	0.352	1
2	3-Chlorobiphenyl	0.209	1
3	4-Chlorobiphenyl	0.222	1

Reviewing Results

MiST Ranks the Similarity of Each Reference Mixture to the Candidate Mixture

MiST

Mixtures Similarity Tool

Version 1.1
Version Date: 2/18/2022

Run Date
2/18/2022

Run Settings

Use equal or unequal potencies?	Unequal
Critical value (optional)	
Data rich or data poor	Data rich
Candidate mixture name:	AR 1254
Number of Reference Mixtures:	3

Candidate Mixture	**AR 1254**
BMD	25.855
ED	77.56
Nearest Reference	AR 1242
Distance Dw (mean)	14.659

Chemical #	Name	Potencies	Mass Fraction
1	2-Chlorobiphenyl	1.28802283	0
2	3-Chlorobiphenyl	0.764763556	0
3	4-Chlorobiphenyl	0.81233258	0
4	2,2'-Dichlorobiphenyl	1.423411594	0.000600841
5	2,3-Dichlorobiphenyl	1.353887634	0

MiST Results

Candidate Mixture	AR 1254
BMD	25.855
ED	77.56
Nearest Reference	AR 1242
Distance Dw (mean)	14.659

Reference Mixture	AR 1242
BMD	34.564
ED	103.69
Delta	69.126
Dw (Mean)	14.659
Dw (Upper 95th)	58.298
Conclusion	Acceptable
Rank	1

Reference Mixture	AR 1260
BMD	19.364
ED	58.09
Delta	51.705
Dw (Mean)	40.381
Dw (Upper 95th)	310.392
Conclusion	Not Acceptable
Rank	2

Reference Mixture	AR 1016
BMD	110.38
ED	331.14
Delta	220.76
Dw (Mean)	3582.754
Dw (Upper 95th)	34458.203
Conclusion	Not Acceptable
Rank	3

For each reference mixture, MiST Returns the following information:

BMD: If mean and SD were entered, the mean BMD is returned. If a CDF was entered, the 50th percentile is returned.

ED: The effective dose entered for each reference mixture is returned.

Delta: the critical value for the analysis, set to |ED - BMD| by default.

Dw (Mean): the average Euclidean distance between the reference mixture and the candidate mixture.

Dw (Upper 95th): the 95th percentile of the Euclidean distance between the reference mixture and the candidate mixture.

Interpreting MiST Results

Candidate Mixture	AR 1254
BMD	25.855
ED	77.56
Nearest Reference	AR 1242
Distance Dw (mean)	14.659

Reference Mixture	AR 1242
BMD	34.564
ED	103.69
Delta	69.126
Dw (Mean)	14.659
Dw (Upper 95th)	58.298
Conclusion	Acceptable
Rank	1

Reference Mixture	AR 1260
BMD	19.364
ED	58.09
Delta	51.705
Dw (Mean)	40.381
Dw (Upper 95th)	310.392
Conclusion	Not Acceptable
Rank	2

Reference Mixture	AR 1016
BMD	110.38
ED	331.14
Delta	220.76
Dw (Mean)	3582.754
Dw (Upper 95th)	34458.203
Conclusion	Not Acceptable
Rank	3

Conclusion:

Acceptable: the Dw (Upper 95th) value for the reference mixture is less than the critical value (Delta); consider the reference mixture as SIMILAR to the candidate mixture.

Not Acceptable: The Dw (Upper 95th) value for the reference mixture is greater than the critical value (Delta); unable to claim that the reference mixture is similar to the candidate mixture.

Rank: When several reference mixtures are considered similar to the candidate mixture, the rank indicates which reference mixture is the best match to the candidate mixture. This is determined by comparing the Dw (Mean) for each reference mixture.

Summary

MiST is a Microsoft Excel-Based tool developed to support risk assessment of PCB mixtures relevant to human health.

MiST uses a Monte Carlo-based approach to account for the uncertainty in candidate and reference BMDs.

MiST ascertains the degree to which “candidate mixtures” and “reference mixtures” are similar from a toxicity standpoint.

Contributors

Coding and adaptation of Marshall Methodology	User Guide and Tool	MiST Validation	MiST Visuals and User Guide Formatting
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