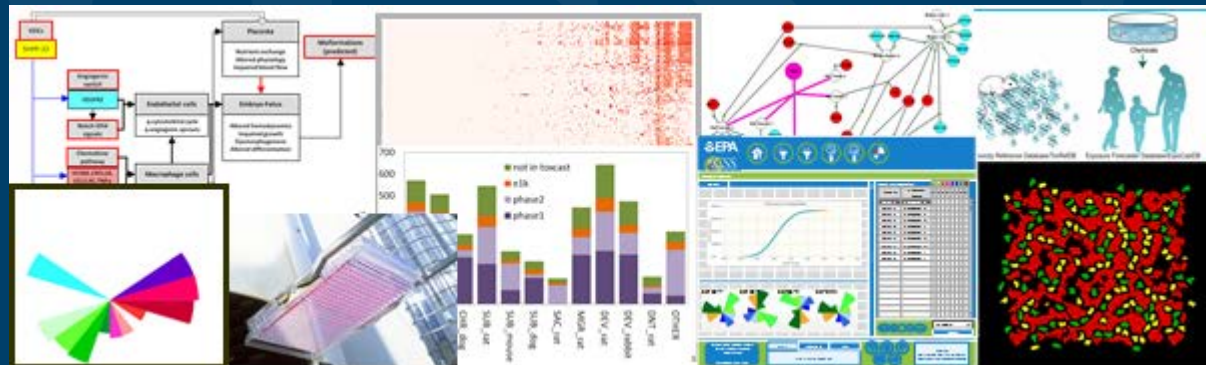


Update on NCCT Prioritization Activities



August 28, 2017

Russell Thomas
Director
National Center for Computational Toxicology
Office of Research and Development
U.S. Environmental Protection Agency

Objective

To develop the data infrastructure and a flexible tool that enables chemical prioritization across a broad-range of decision contexts and regulatory frameworks.

Initial Prioritization Applications and Decision Contexts

Non-Food Pesticidal Inerts

Decision Context: **Prioritize** non-food use inert ingredients for additional study

Regulatory Partner: OPP
Chemicals: 126

Desired Components:

- Phys-Chem properties
- Environmental fate and transport
- Human Health Hazard (Chronic)
- Alternative Hazard Data (*in vitro/in silico*)
- Toxicokinetic data (*in vivo* and *in vitro*)
- Consumer and industrial use

TSCA Chemicals

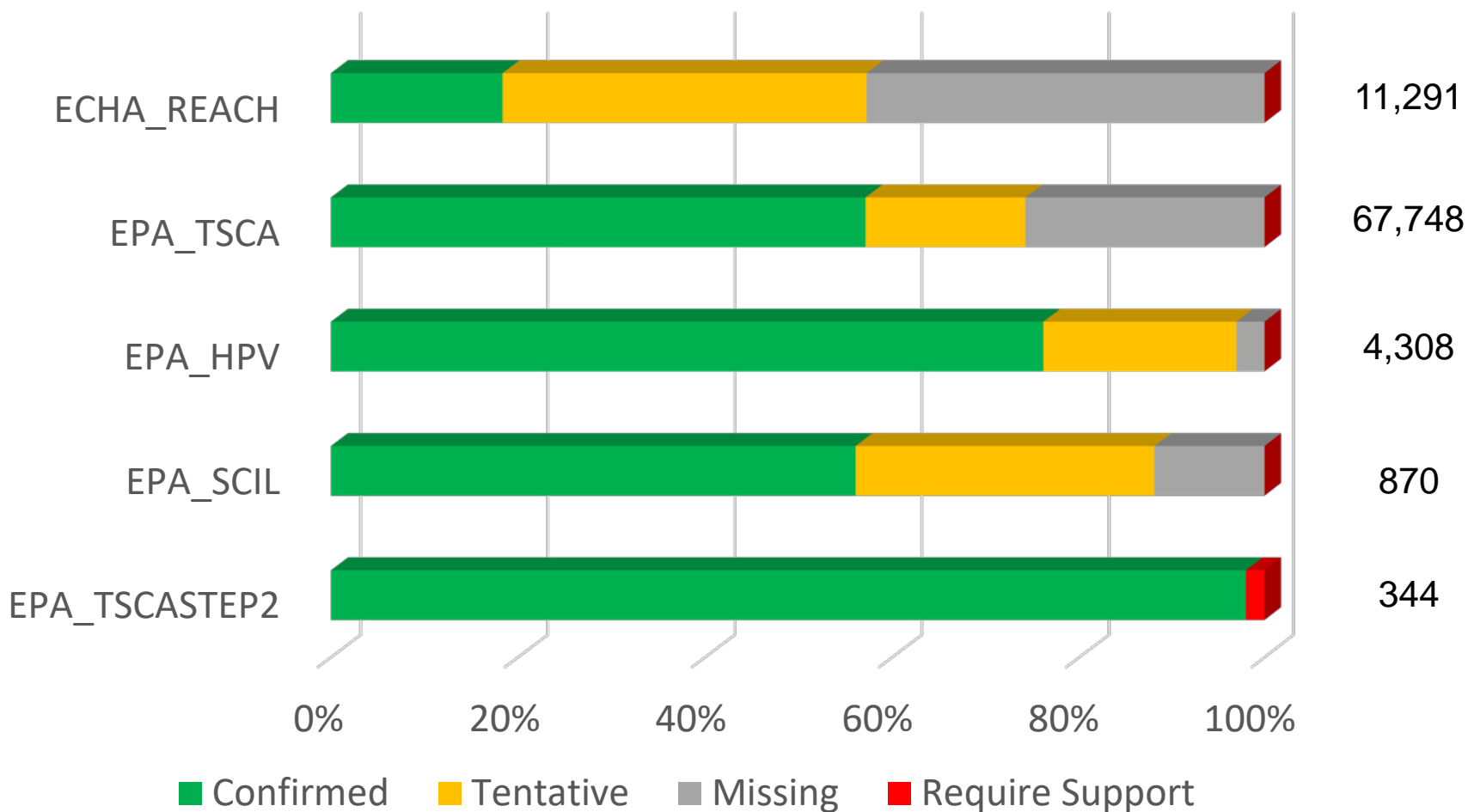
Decision Context: **Pre-prioritize** chemicals for new TSCA legislation

Regulatory Partner: OCSPP
Chemicals: Initially ~5,000

Desired Components:

- Phys-Chem properties
- Human Health Hazard
- Ecological Hazard
- Alternative Hazard Data (*in vitro/in silico*)
- Toxicokinetic Data (*in vivo* and *in vitro*)
- Persistence/Bioaccumulation potential
- Environmental fate/transport
- Exposure
- Consumer and industrial use

Chemical Domain and List Curation



Initial Data Domains

Human Health Hazard	Eco Hazard	Persistence/Bioaccumulation	Exposure
In Vivo subacute NOAEL	ECOTOX Acute Aquatic	Biodegradation (Physprop)	OSHA (Number of NAICS codes)
In Vivo subchronic NOAEL	ECOTOX Chronic Aquatic	BCF (PhysProp)	OSHA (Number of SIC codes)
In Vivo chronic NOAEL	ECOTOX Repro Aquatic	BAF (PhysProp)	Consumer Product count
In Vivo repro/mgr NOAEL	ECOTOX Acute Terrestrial	Atmospheric Oxidation	Child Use Product count
In Vivo dev NOAEL	ECOTOX Chronic Terrestrial	Soil Adsorp. Coeff.	CDR Production Volume
In Vivo Acute Toxicity	ECOTOX Repro Terrtrial	Fish Biotrans. Half-life	NHANES (median value)
Skin Sensitization			NHANES (95th percentile)
Genotox Data			OPPT Monitoring (Biomonitoring Count)
ToxCast Most Sensitive AC50			OPPT Monitoring (Ambient Air Count)
Stemina DevTox Hit Call			OPPT Monitoring (Indoor Air Count)
Tanguay Zebrafish Hit Call			OPPT Monitoring (Drinking Water Count)
Padilla Zebrafish Hit Call			OPPT Monitoring (Waste Water Count)
Acute Neurotox MEA			OPPT Monitoring (Sediment Count)
DNT MEA			OPPT Monitoring (Food Count)
ToxCast ACHE			OPPT Monitoring (Vegetation Count)
Tox21 ACHE			OPPT Monitoring (Ground Water Count)
ToxCast ER Model			OPPT Monitoring (Surface Water Count)
ToxCast AR Model			OPPT Monitoring (Soil Count)
			OPPT Monitoring (Wildlife/Fish Count)
			OPPT Monitoring (Wildlife/Aq. Invert. Count)
			OPPT Monitoring (Landfill Leachate Count)
			OPPT Monitoring (Other Count)

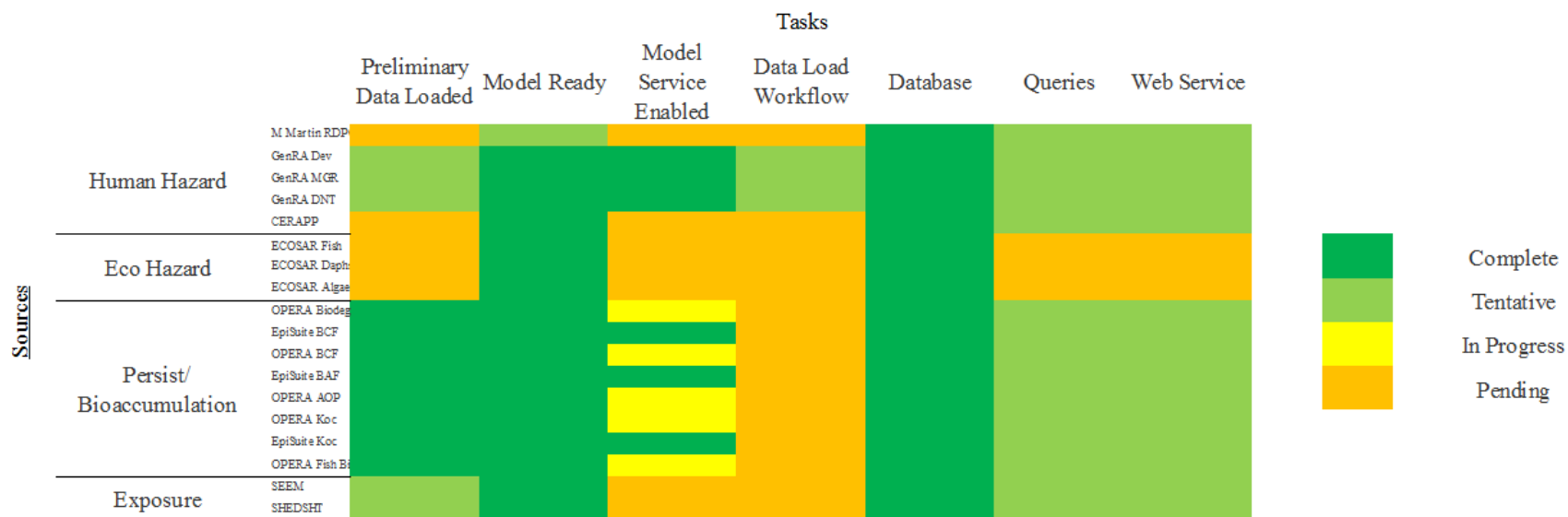
Progress on Assembly and Curation of Initial Measured/Reported Data



Initial Model Data Queue

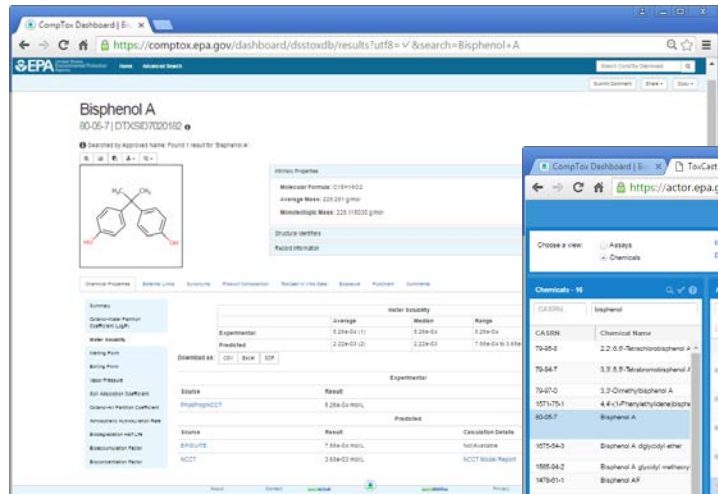
Human Health Hazard	Eco Hazard	Persistence/Bioaccumulation	Exposure
NCCT Systemic Tox NOAEL	ECOSAR Fish	OPERA Biodeg	SEEM
GenRA Dev	ECOSAR Daphnia	EpiSuite BCF	SHEDS-HT
GenRA MGR	ECOSAR Algae	OPERA BCF	
GenRA DNT		EpiSuite BAF	
CERAPP ER Activity		OPERA AOP	
		OPERA Koc	
		EpiSuite Koc	
		OPERA Fish Biotrans	

Progress on Assembly and Curation of Initial Model Data



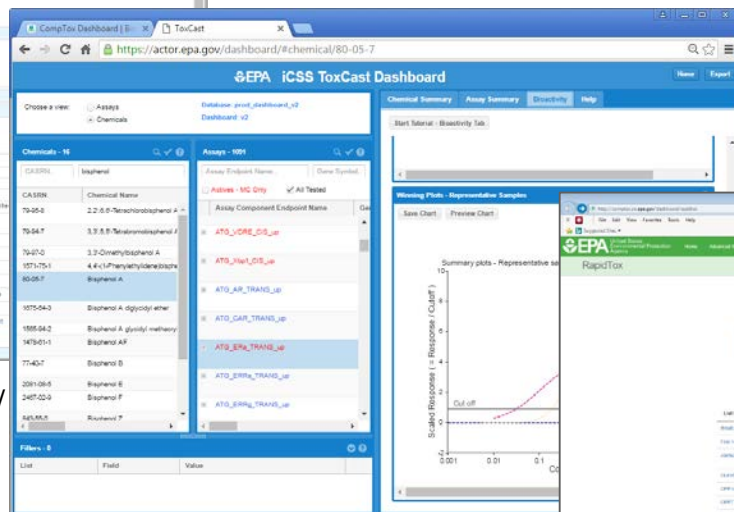
A Portfolio of Tools to Deliver Data and Provide Decision Support

Comptox Chemistry Dashboard



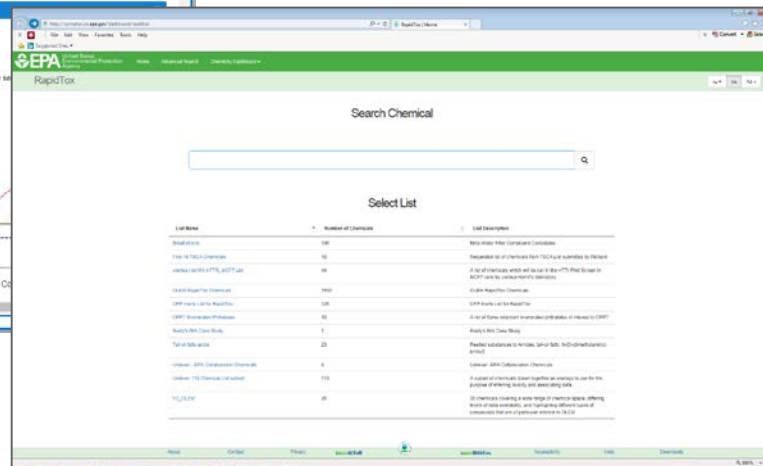
<https://comptox.epa.gov/dashboard/>

ToxCast Dashboard



<https://actor.epa.gov/dashboard/>

RapidTox Dashboard



Screening
Assessments

Chemical
Prioritization

...

Screen Shots of RapidTox Prioritization Tool in Development

RapidTox Prioritization Workflow x RapidTox: Bisphenol A x +

127.0.0.1:4499
90%
Search

Google Scholar
RapidTox Report Index
Washington Post: Bre...
The New York Times
phpMyAdmin
My Drive - Google Drive
Home - PubMed - NCBI
System Dashboard - JI...
Dashbo

RapidTox Prioritization Workflow

Chemical List:
☒ TSCA
☐ OPP Inerts

To run prioritization, select the chemical set, the allowable data domains, and update the weights. Then select the Recalculate button and go to the prioritization tab. You can then sort by the different prioritization types.

Recalculate
Export Table

Components
Weighting Factors
In Vivo Data
PhysChem Data
ER Data
AR Data
ER QSAR Data
Hazard Prioritization

Exposure Prioritization
Overall Prioritization

Check All
Uncheck All

Human Health

Acute	Subchronic	Chronic	DevTox	ReproTox	Cancer	Mutagenicity	Neurotox	Systemic Tox Models
<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> Martin model
<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> Pradeep model
								<input checked="" type="checkbox"/> GenRA model
								<input checked="" type="checkbox"/> ToxCast IVIVE

Endocrine

Estrogen Agonist	Estrogen Antagonist	Androgen Agonist	Androgen Agonist
<input checked="" type="checkbox"/> In vitro	<input checked="" type="checkbox"/> In vitro	<input checked="" type="checkbox"/> In vitro	<input checked="" type="checkbox"/> In vitro
<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR

Ecological

Fish Acute Tox	Crustacea Acute Tox	Algae Tox	Fish ReproTox
<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> In vivo	<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR
<input checked="" type="checkbox"/> QSAR	<input checked="" type="checkbox"/> QSAR		

Three Prioritization Methods Initially Implemented

Expanded TSCA 2012

- Add up maximum score from each domain (hazard, exposure, physchem)
- Expanded suite of *in vivo* hazard databases
- Apply NAM when traditional *in vivo* data is not available (i.e., ToxCast+HTTK and GenRA)
- Included endocrine-related effects (ER and AR)
- Included quantitative exposure models and expanded suite of exposure databases
- Flag chemicals with data gaps
- Categorical bins
 - High: 7-9
 - Moderate: 5-6
 - Low: 3-4

Sum of Scores (SOS)

- Modified from TSCA 2012 method
- Sums scores within and across domains
- Ordinal ranking

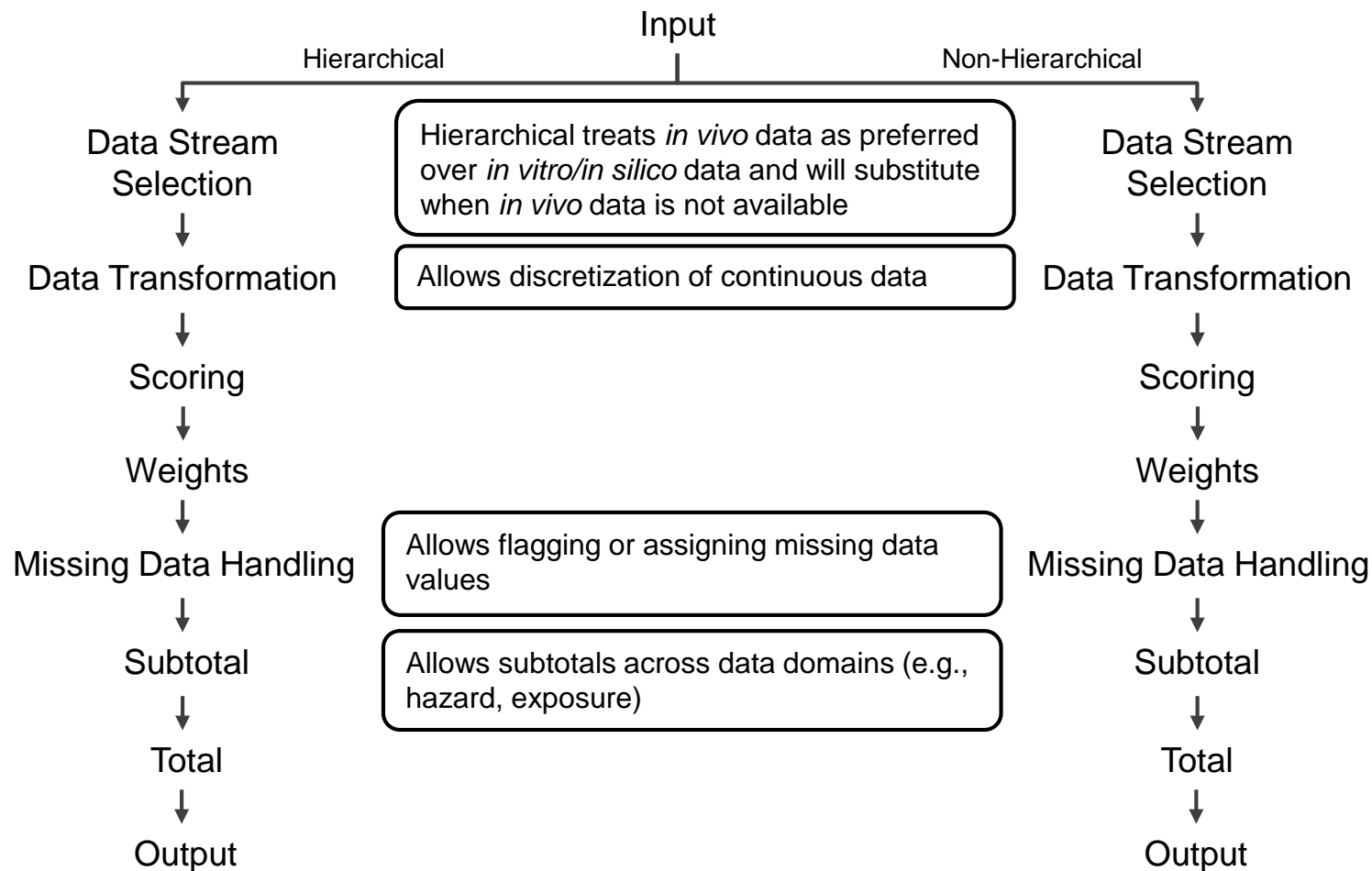
Hazard Exposure Ratio

- Minimum oral POD to exposure ratio
- Apply NAM when traditional *in vivo* data is not available
- Categorical bins
 - High: $<10^4$ HER
 - Moderate: $10^4 - 10^5$ HER
 - Low: $>10^6$ HER

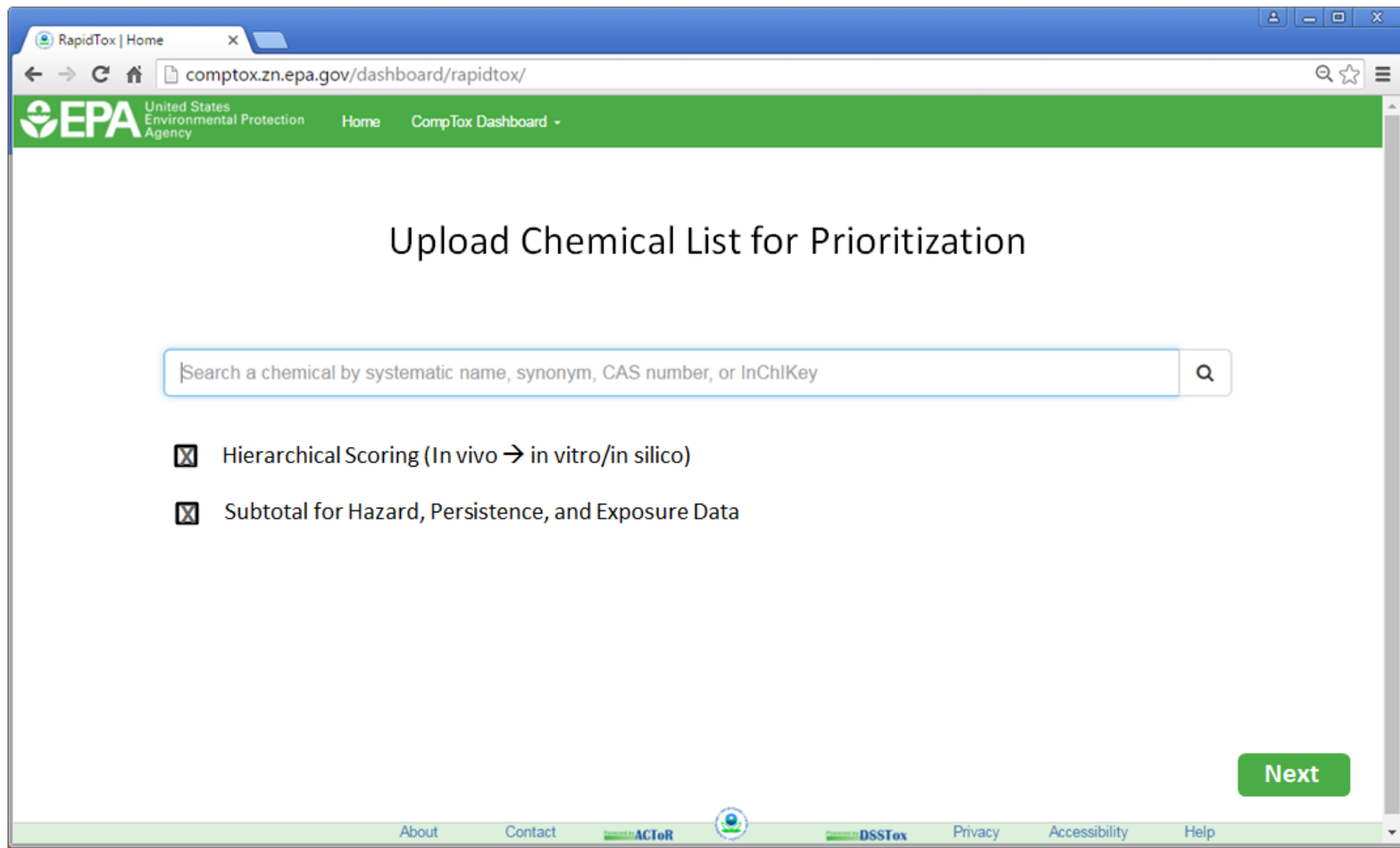
Ongoing Activities

- Continue chemical and data curation efforts
- Prepare to release prototype prioritization tool to internal partners
- Work with regulatory partners to test and refine prototype
- Design and scope next generation prioritization tool

Tentative Workflow for the Next Generation Tool




Mock Up of the Next Generation Interface



The screenshot shows a web browser window with the URL `comptox.zn.epa.gov/dashboard/rapidtox/`. The page features a green header with the EPA logo and navigation links for 'Home' and 'CompTox Dashboard'. The main content area is titled 'Upload Chemical List for Prioritization' and includes a search bar with the placeholder text 'Search a chemical by systematic name, synonym, CAS number, or InChIKey'. Below the search bar are two checked checkboxes: 'Hierarchical Scoring (In vivo → in vitro/in silico)' and 'Subtotal for Hazard, Persistence, and Exposure Data'. A green 'Next' button is located in the bottom right corner. The footer contains links for 'About', 'Contact', 'ACToR', 'DSSTox', 'Privacy', 'Accessibility', and 'Help'.

RapidTox | Home

← → ↻ 🏠 `comptox.zn.epa.gov/dashboard/rapidtox/` 🔍 ☆ ☰



 United States Environmental Protection Agency Home CompTox Dashboard ▾

Upload Chemical List for Prioritization

Search a chemical by systematic name, synonym, CAS number, or InChIKey 🔍

- ☒ Hierarchical Scoring (In vivo → in vitro/in silico)
- ☒ Subtotal for Hazard, Persistence, and Exposure Data

Next

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Mock Up of the Hierarchical Workflow (Data Selection)

RapidTox | Home
comptox.zn.epa.gov/dashboard/rapidtox/

EPA United States Environmental Protection Agency
Home CompTox Dashboard

Data

Human Hazard

☒ *In Vivo* Acute (LD50)
☒ *In Vivo* Subacute (NOAEL/LOAEL)
☒ *In Vivo* Subchronic (NOAEL/LOAEL)
☒ *In Vivo* Chronic (NOAEL/LOAEL)
☒ *In Vivo* Developmental (NOAEL/LOAEL)
☒ *In Vivo* Reproductive (NOAEL/LOAEL)

☒ *In Vivo* Skin Sensitization*
☒ Genotoxicity*
☒ *In Vitro* Bioactivity or *In Silico* RDT Model
☒ *In Vitro* Neurotox* (ToxCast/Tox21 Integrated Call)
☒ *In Vitro* ER Activity* (ToxCast Model)
☒ *In Silico* ER Activity*
☒ *In Vitro* Stemina* or *In Silico* DevTox GenRA*
☒ *In Silico* ReproTox GenRA*

Ecological Hazard

☒ *In Vivo* Acute Aquatic (LC50)
☒ *In Vivo* Chronic Aquatic (EC50)
☒ *In Vivo* Repro Aquatic (EC50)
☒ *In Vivo* Acute Terrestrial (LD50)
☒ *In Vivo* Chronic Terrestrial (EC50)
☒ *In Vivo* Repro Terrestrial (EC50)

☒ *In Silico* Acute Aquatic (LC50)

Persistence and Bioaccumulation

☒ Exp Biodegradation
☒ Exp Bioconc Factor
☒ Exp Bioaccum Factor
☒ Exp Atmos Oxidation
☒ Exp Soil Adsorp Coefficient
☒ Exp Fish Biotrans Half Life

☒ *In Silico* Biodeg
☒ *In Silico* BCF
☒ *In Silico* Bioaccum Factor
☒ *In Silico* Atmos Oxid
☒ *In Silico* Soil Adsorp
☒ *In Silico* Fish Biotrans

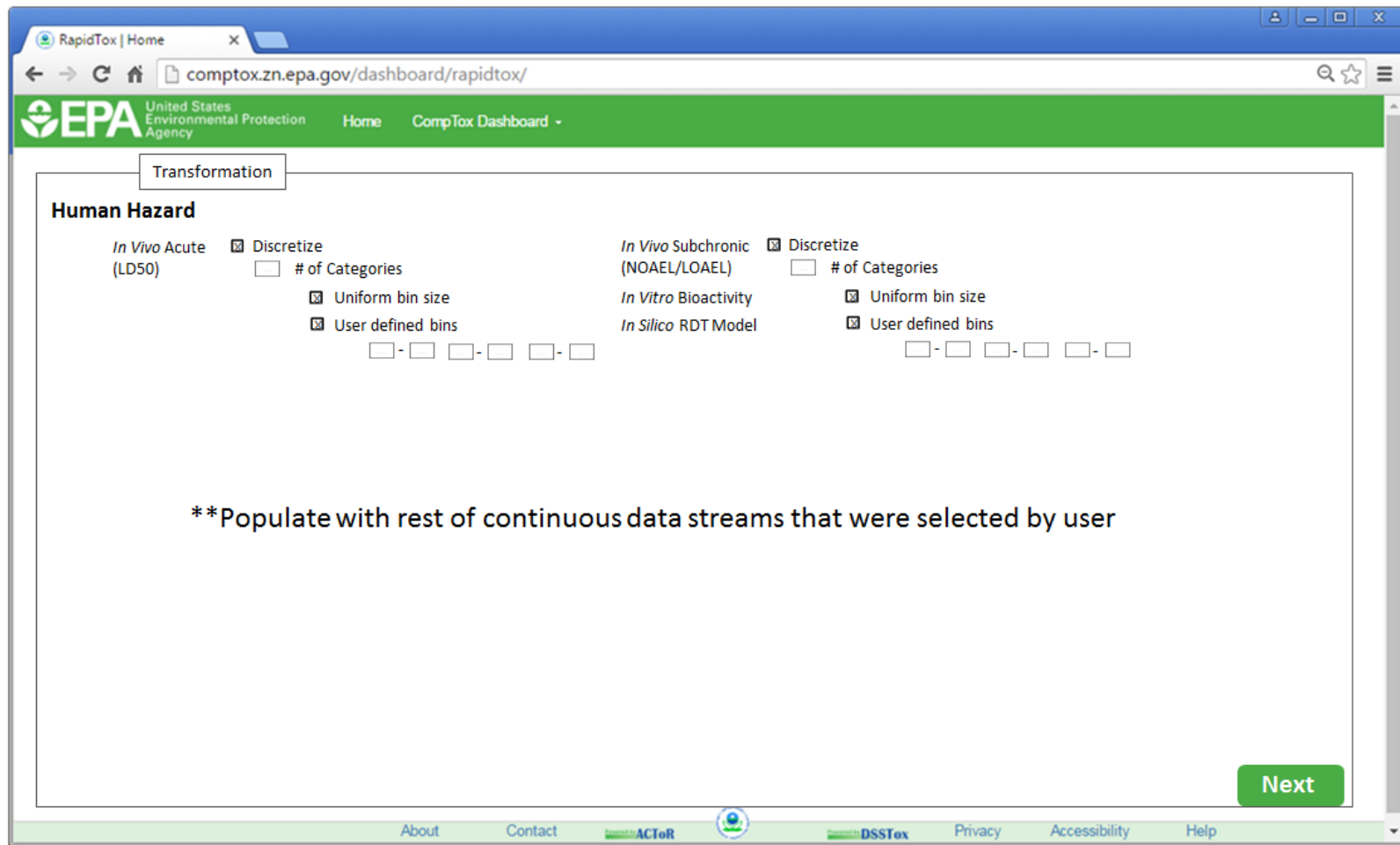
*Denotes binary (yes/no) data.
Next

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*Other data streams (e.g., exposure) not shown.

Skip to End

Mock Up of the Hierarchical Workflow (Transformation)



The screenshot shows a web browser window with the URL `comptox.zn.epa.gov/dashboard/rapidtox/`. The page has a green header with the EPA logo and navigation links for Home and CompTox Dashboard. A 'Transformation' tab is selected. The main content area is titled 'Human Hazard' and contains two columns of options for data transformation. Each column has a 'Discretize' checkbox (checked), a '# of Categories' input field, and two checked checkboxes for 'Uniform bin size' and 'User defined bins'. Below these are three input fields for defining bins. A large text instruction states: '**Populate with rest of continuous data streams that were selected by user'. A green 'Next' button is in the bottom right. The footer includes links for About, Contact, ACToR, DSSTox, Privacy, Accessibility, and Help.

Transformation

Human Hazard

<i>In Vivo</i> Acute (LD50)	<input checked="" type="checkbox"/> Discretize	<i>In Vivo</i> Subchronic (NOAEL/LOAEL)	<input checked="" type="checkbox"/> Discretize
	<input type="checkbox"/> # of Categories		<input type="checkbox"/> # of Categories
	<input checked="" type="checkbox"/> Uniform bin size		<input checked="" type="checkbox"/> Uniform bin size
	<input checked="" type="checkbox"/> User defined bins		<input checked="" type="checkbox"/> User defined bins
	<input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/>		<input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/>

**Populate with rest of continuous data streams that were selected by user

Next

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Mock Up of the Hierarchical Workflow (Scoring)

RapidTox | Home

comptox.zn.epa.gov/dashboard/rapidtox/

EPA United States Environmental Protection Agency Home CompTox Dashboard

Scoring

Human Hazard

In Vivo Acute (LD50)

☒ Max/Value

☒ log10 Max/Value

☒ User defined

☐ X-X

☐ Y-Y

☐ Z-Z

In Vivo Reproductive (NOAEL/LOAEL)

☒ Max/Value

☒ log10 Max/Value

☒ User defined

☐ X-X

☐ Y-Y

☐ Z-Z

In Vivo Subchronic (NOAEL/LOAEL)

☒ Max/Value

☒ log10 Max/Value

☒ User defined

☐ X-X

☐ Y-Y

☐ Z-Z

In Vitro Bioactivity

☐ X-X

☐ Y-Y

☐ Z-Z

In Silico RDT Model

☐ X-X

☐ Y-Y

☐ Z-Z

Genotoxicity*

☒ User defined

☐ Y ☐ N

☒ Set Y to max hazard score (all data selected), N to min hazard score

In Silico ReproTox GenRA*

☒ Set to max of *in vivo* NOAEL/LOAEL

☒ Set to median of *in vivo* NOAEL/LOAEL

☒ Set to average of *in vivo* NOAEL/LOAEL

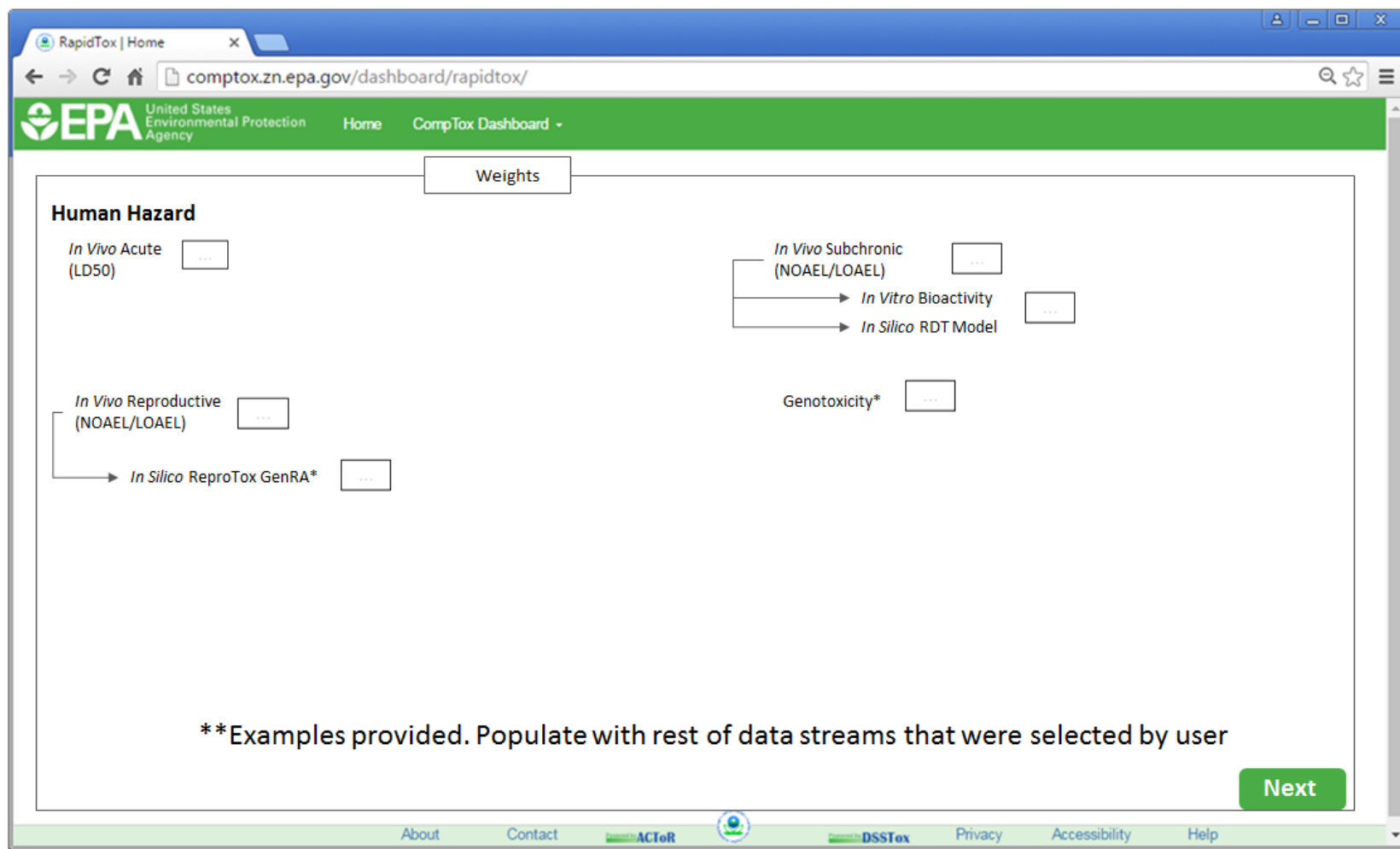
☒ Set to user defined value

**Examples provided. Populate with rest of data streams that were selected by user

Next

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Mock Up of the Hierarchical Workflow (Weights)



Mock Up of the Hierarchical Workflow (Missing Data)

RapidTox | Home

comptox.zn.epa.gov/dashboard/rapidtox/

 United States Environmental Protection Agency Home CompTox Dashboard

Missing Data

Human Hazard

In Vivo Acute (LD50)

- ☒ Flag Missing Data
- ☒ Flag Missing Data and Set to Max Score Across Chemicals
- ☒ Flag Missing Data and Set to User Defined Value

In Vivo Reproductive (NOAEL/LOAEL)

- ☒ Flag Missing Data

In Silico ReproTox GenRA*

- ☒ Flag Missing Data
- ☒ Flag Missing Data and Set to Max Score Across Chemicals
- ☒ Flag Missing Data and Set to User Defined Value

In Vivo Subchronic (NOAEL/LOAEL)

- ☒ Flag Missing Data

In Vitro Bioactivity

- ☒ Flag Missing Data
- ☒ Flag Missing Data and Set to Max Score Across Chemicals
- ☒ Flag Missing Data and Set to User Defined Value



In Silico RDT Model

Genotoxicity*

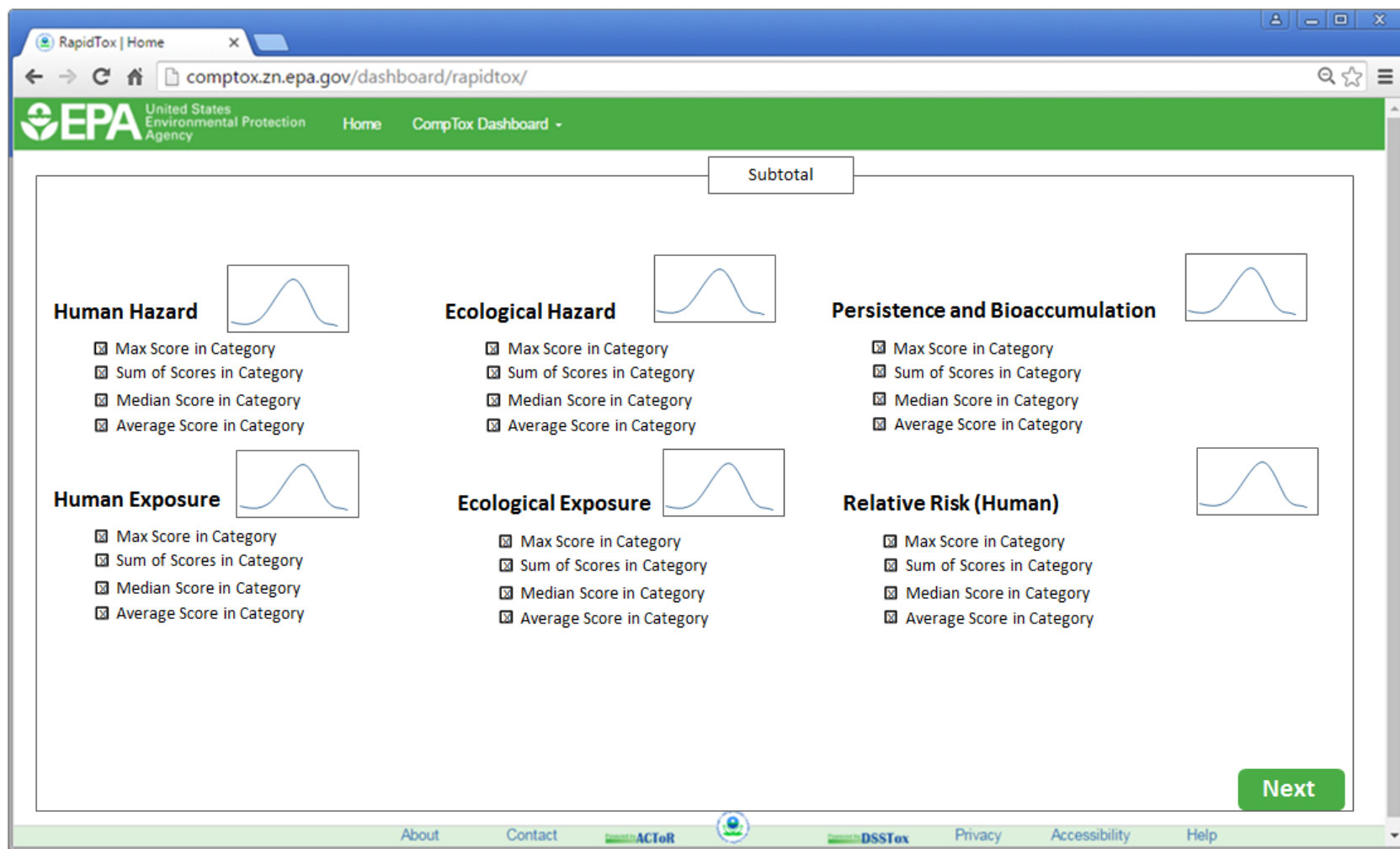
- ☒ Flag Missing Data
- ☒ Flag Missing Data and Set to Max Score Across Chemicals
- ☒ Flag Missing Data and Set to User Defined Value

****Examples provided. Populate with rest of data streams that were selected by user**

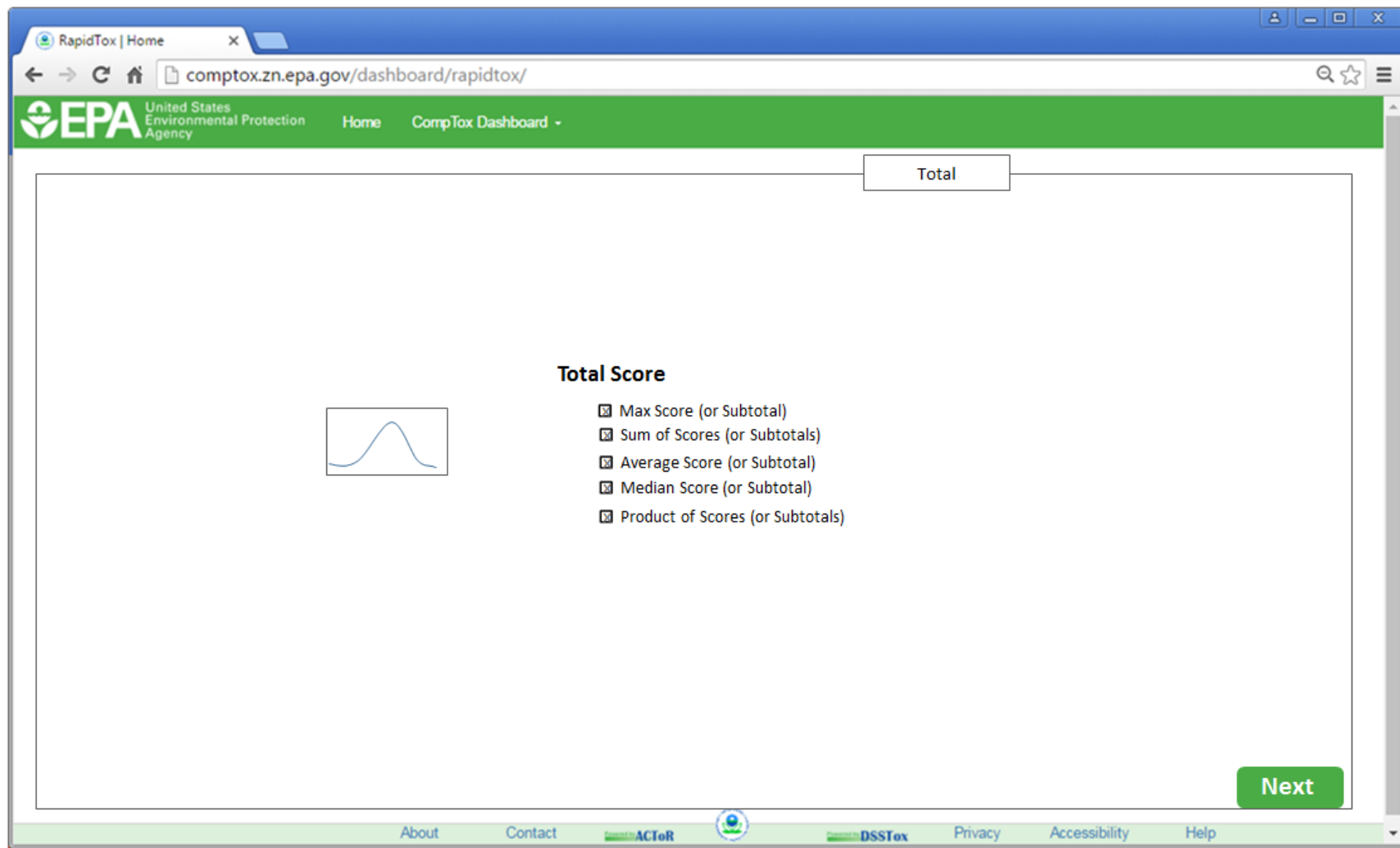
Next

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Mock Up of the Hierarchical Workflow (Subtotal)





Mock Up of the Next Generation Interface (Totaling)

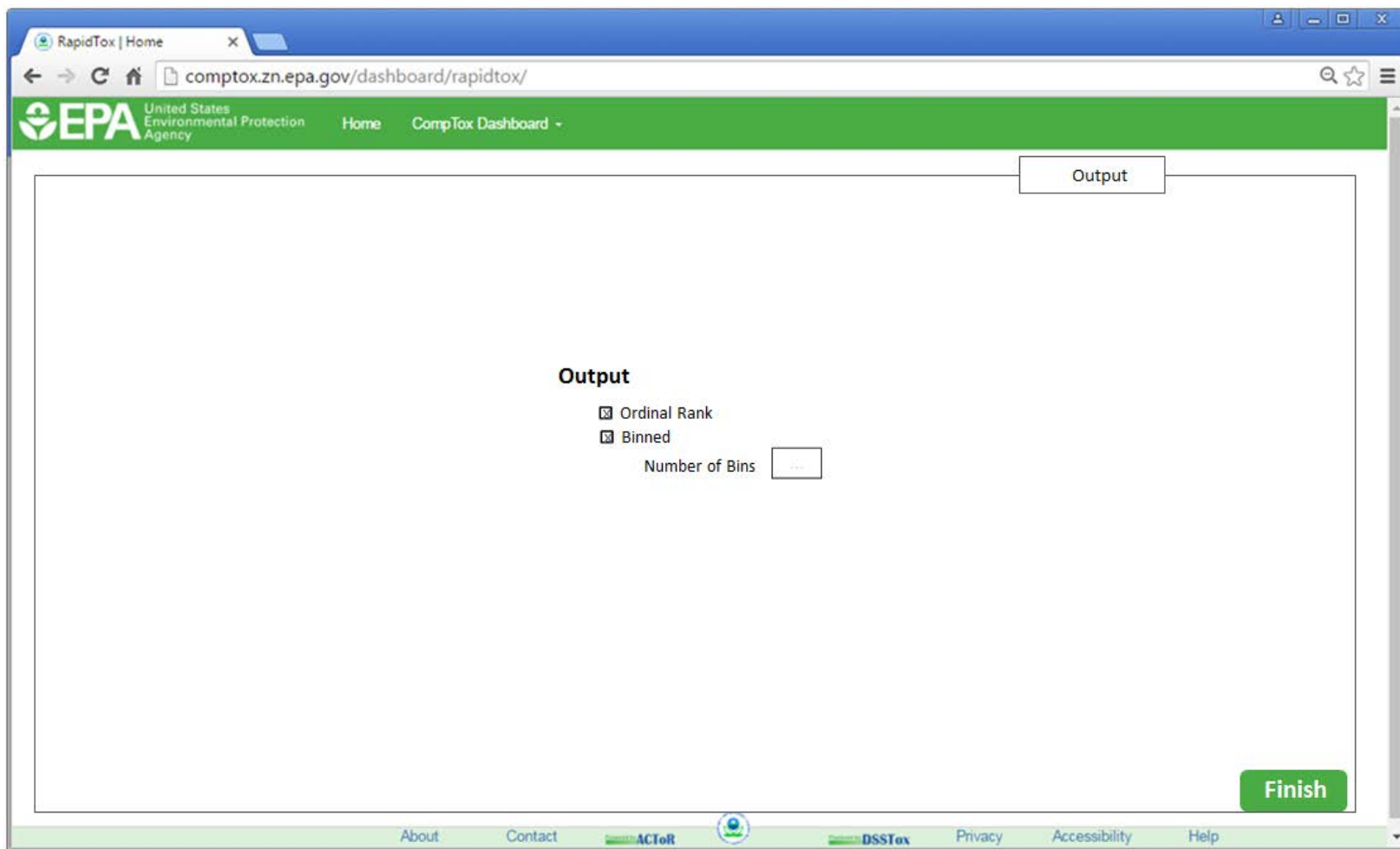


The mockup shows a web browser window with the following elements:

- Browser Tab:** RapidTox | Home
- Address Bar:** comptox.zn.epa.gov/dashboard/rapidtox/
- Header:** EPA United States Environmental Protection Agency. Navigation links: Home, CompTox Dashboard.
- Main Content Area:**
 - Total:** A box containing the word "Total".
 - Total Score:** A section with a bell curve icon and a list of five checkboxes, all of which are checked:
 - ☒ Max Score (or Subtotal)
 - ☒ Sum of Scores (or Subtotals)
 - ☒ Average Score (or Subtotal)
 - ☒ Median Score (or Subtotal)
 - ☒ Product of Scores (or Subtotals)
 - Next:** A green button in the bottom right corner.

- Footer:** A row of links: About, Contact,  ACToR,  DSSTox, Privacy, Accessibility, Help.

Mock Up of the Hierarchical Workflow (Output)

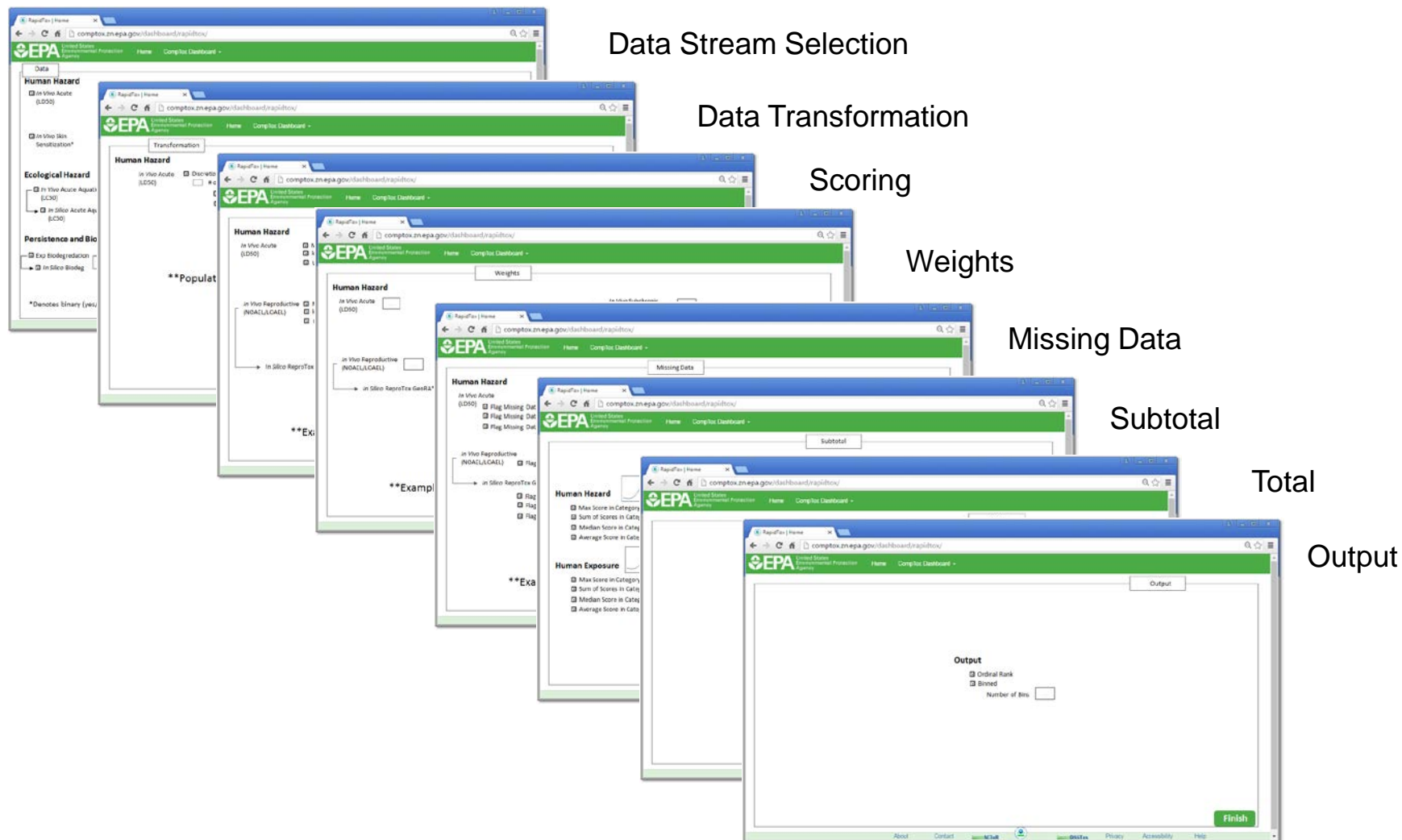


The screenshot shows a web browser window with the URL `comptox.zn.epa.gov/dashboard/rapidtox/`. The page features a green header with the EPA logo and navigation links for Home and CompTox Dashboard. The main content area is titled "Output" and contains a form with the following elements:

- ☒ Ordinal Rank
- ☒ Binned
- Number of Bins:

A green "Finish" button is located in the bottom right corner of the main content area. The footer contains links for About, Contact, ACToR, DSSTox, Privacy, Accessibility, and Help.

Mock Up of the Hierarchical Workflow



Opportunities for International Collaboration

- Exchange, curate, and harmonize non-confidential summary data (e.g., human/eco hazard, persistence, bioaccumulation potential)
- Build shared data warehouse
- Joint development of prioritization tool or input on tool development