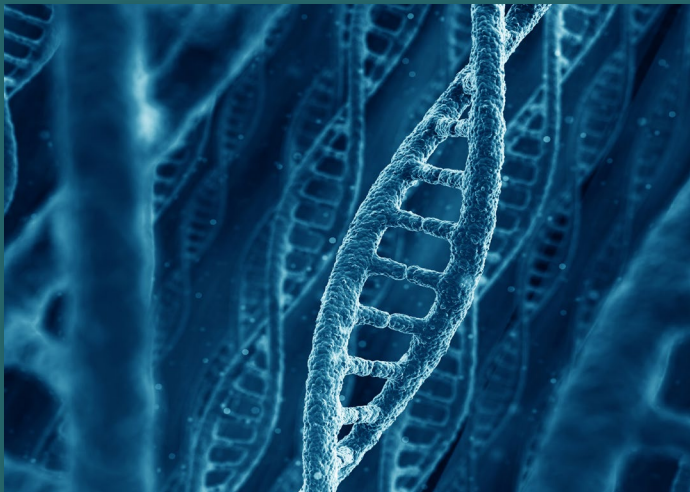# Case Study Results

Shintaro Hagiwara, Ph.D.
Risk Sciences International

The views expressed in this presentation are those of the presenters and do not necessarily reflect the views or policies of the U.S. EPA

Outline

- Baseline analysis scenarios

  - Results for the BRDM
  - Results for the TRDM

- Sensitivity analysis scenarios

  - Effect of the quality of exposure information
  - Effect of the adverse health outcome and cost of control
  - Effect of the toxicity distribution
  - Effect of the affected population size
  - Effect of the target risk level
  - Discordance as a source of additional uncertainty

- Summary

# BASELINE ANALYSIS FOR THE BENEFIT-RISK DECISION-MAKER (BRDM)

Key VOI Metrics

Metric	Description
EVISI	The expected value of <u>immediate</u> sample information. This is a measure of the value of information if it could be received and <u>immediately</u> update the estimate of risk. [Larger EVISI values are preferred.]
COD	The cost of delay. This is a measure of the reduction in benefit associated with the <u>delay</u> in the decision-making process. [Smaller COD values are preferred.]
EVDSI = EVISI - COD	The expected value of <u>delayed</u> sample information. This is a measure of the value of the information which combines the quality of the information and the <u>delay</u> associated with it. [Larger EVDSI values are preferred.]
COT	The cost of testing and assessment process. [Smaller COT values are preferred.]
ENBS = EVDSI - COT	The expected net benefit of sampling. This is a measure of the value of the information taking into account the cost of acquiring the information, in addition to its quality and delay properties. The ENBS measures the benefit accrued <u>per testing</u>. [Larger ENBS values are preferred.]
ROI = ENBS / COT	The return on investment. This is a measure of the value of the information expressed as the ratio of the benefit accrued <u>per dollar expended</u>. [Larger ROI values are preferred.]

Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

	ETAP	THHA
ORE (%)		78
EV|CI ($B)		293
EVIPPI ($B)		154
	ETAP	**THHA**
EVISI ($B)	133	143
COD ($B)	12	169
EVDSI ($B)	121	-26
ENBS ($B)	121	-26
ROI	603,877	-6,478
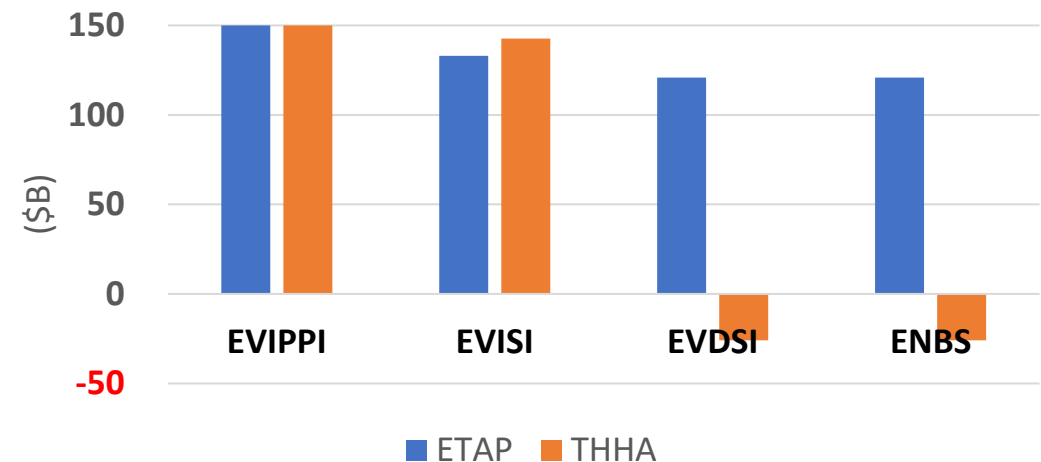
Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

- Minimized ETSC over the 20-year time horizon w/o collecting additional information (EV|CI) = $**293 B**

ORE (%)		78
EV|CI ($B)		293
EVIPPI ($B)		154

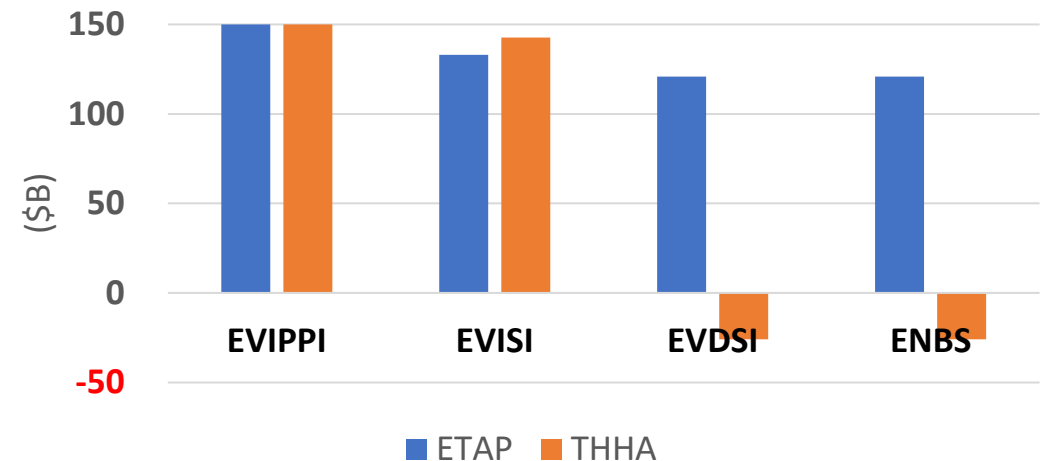|	**ETAP**	**THHA**
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Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

- Minimized ETSC over the 20-year time horizon w/o collecting additional information (EV|CI) = $**293 B**

- Eliminating uncertainty in μ_{tox} will result in a reduction of **$154 B** in ETSC

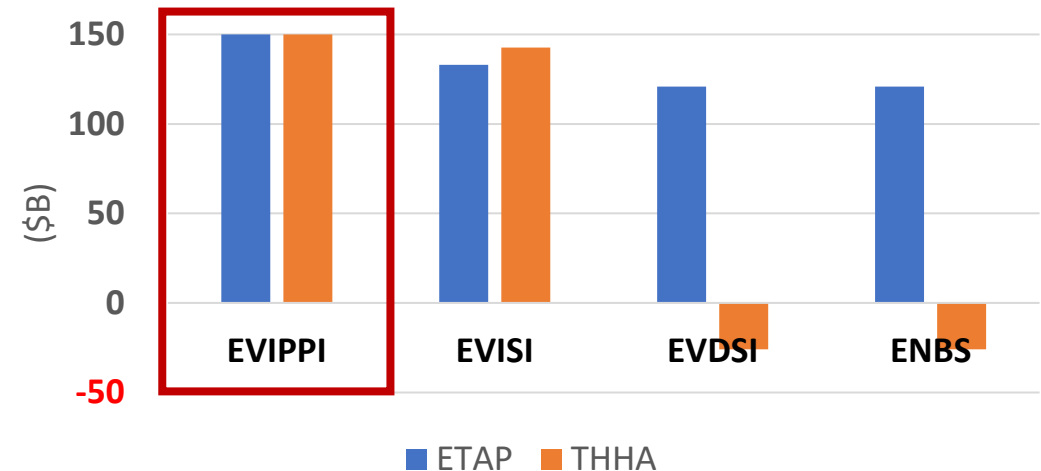|	ETAP	THHA
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- THHA (w/o delay) reduces ETSC by **$143 B**

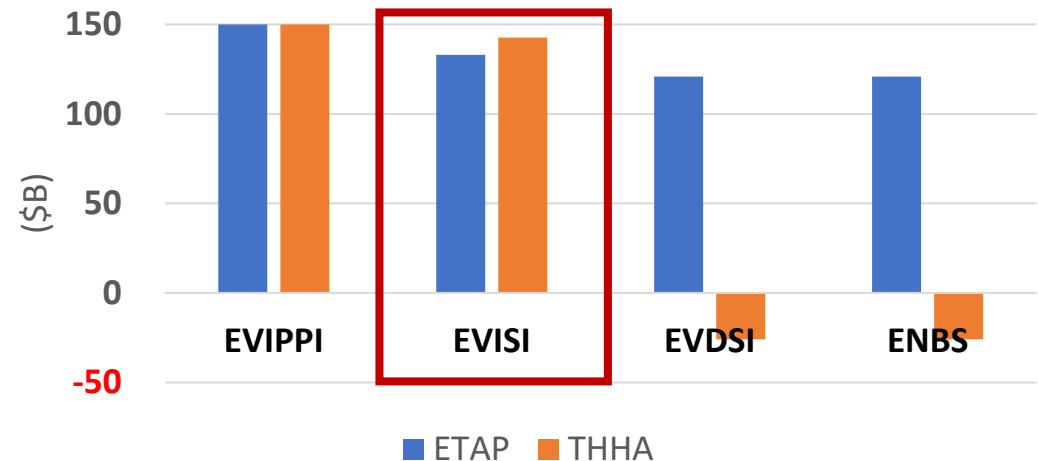|	ETAP	THHA
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- The COD for ETAP (6-months) is **$12 B**
- The COD for THHA (8-year) is **$169 B**

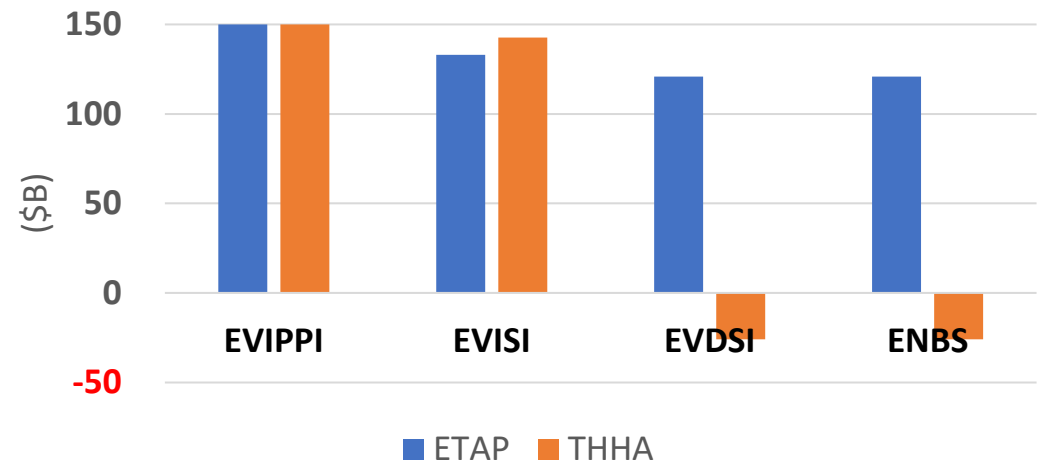|	ETAP	THHA
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- The COD for ETAP (6-months) is **$12 B**
- The COD for THHA (8-year) is **$169 B**

- The EVDSI and ENBS for ETAP is positive at **$121 B**
- The EVDSI and ENBS for THHA is negative at **-$26 B**

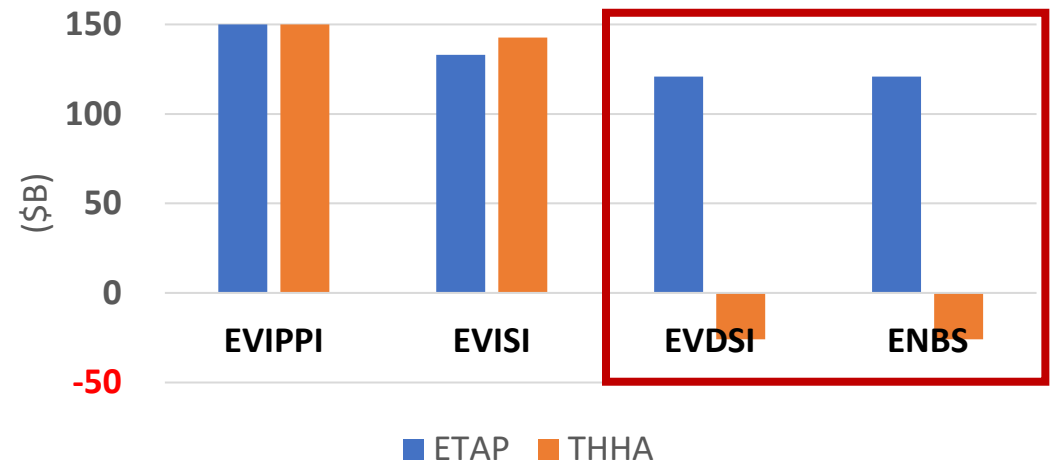|	ETAP	THHA
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- **ETAP provides positive VOI** when the COD and COT are taken into account

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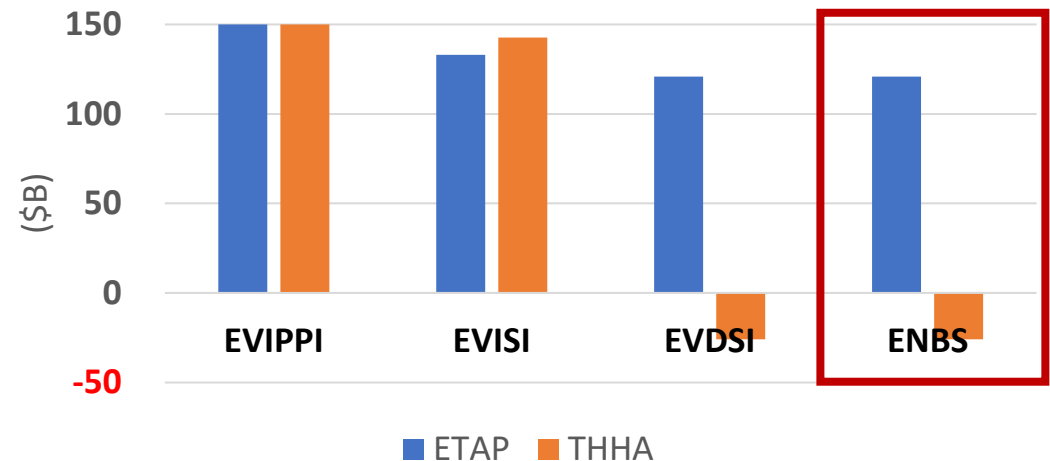
Summary
(BRDM – Baseline Scenarios)

- In 8 out of 9 baseline scenarios, ETAP produced greater delay-adjusted VOI values (EVDSI, ENBS, and ROI) than THHA

- Scenario 9 (high μ_{exp} and high σ_{exp}) led to negative delay-adjusted VOI metrics for both ETAP and THHA due to potentially high prior risk

- A change in μ_{exp} has a greater impact on resulting VOI metrics than a change in σ_{exp}

BASELINE ANALYSIS FOR THE TARGET-RISK DECISION-MAKER (TRDM)

Scenario 5
(Medium μ_{exp} and Medium σ_{exp})
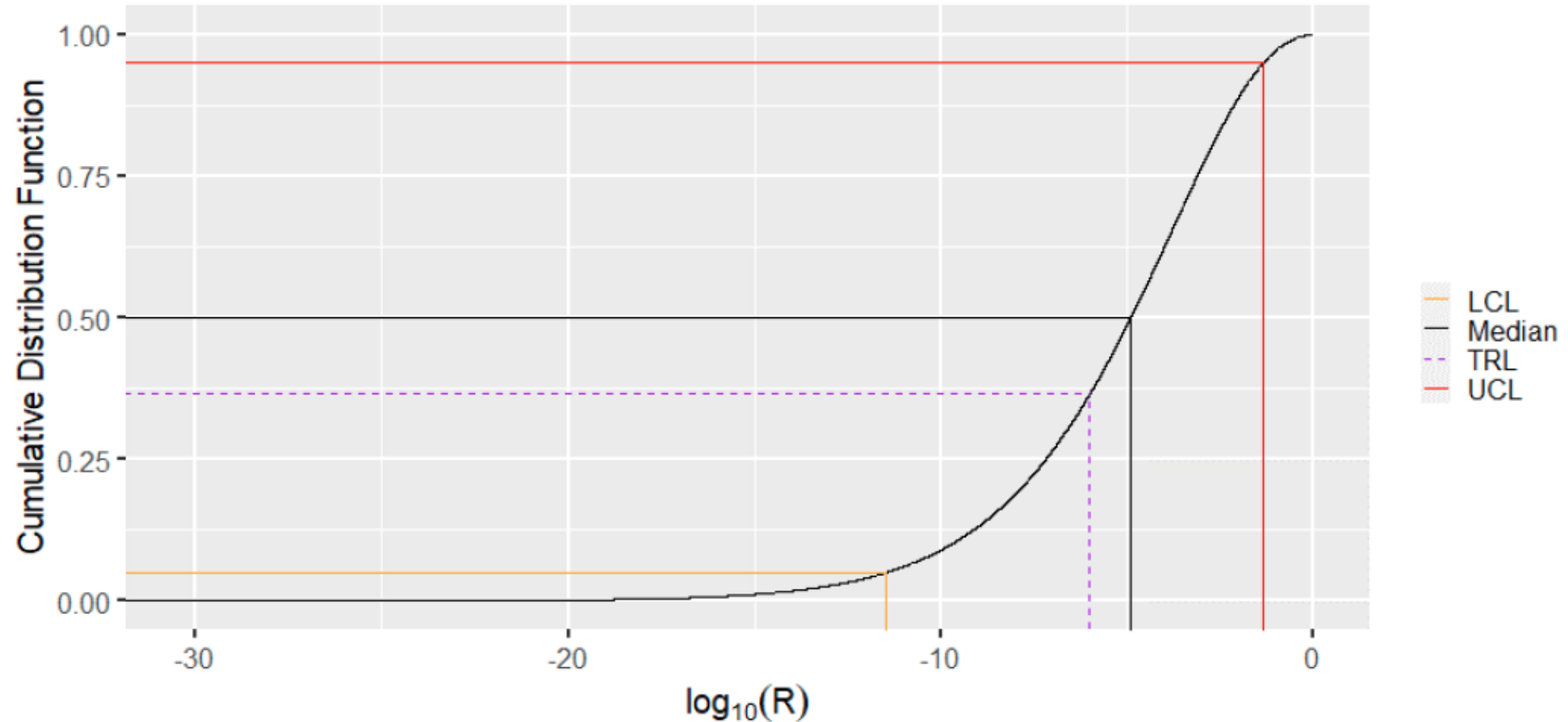
$q_{05} \leq TRL \leq q_{95}$ and therefore the TRDM require additional toxicity testing information

Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

	ETAP	THHA
EV|CI ($B)		446
EVIPPI ($B)		323
EVISI ($B)	297	314
COD ($B)	13	180
EVDSI ($B)	284	135
ENBS ($B)	284	135
ROI	1,420,115	33,678

Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

- ETHC over the 20-year time horizon w/o collecting additional information (EV|CI) = **$446 B**

		ETAP	THHA
EV|CI ($B)			446
EVIPPI ($B)			323
		ETAP	**THHA**
EVISI ($B)		297	314
COD ($B)		13	180
EVDSI ($B)		284	135
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ROI		1,420,115	33,678

Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

- ETHC over the 20-year time horizon w/o collecting additional information (EV|CI) = **$446 B**

- Eliminating uncertainty in μ_{tox} will result in reduction of **$323 B** in ETSC

	ETAP	THHA
EV|CI ($B)		446
EVIPPI ($B)		323
	ETAP	**THHA**
EVISI ($B)	297	314
COD ($B)	13	180
EVDSI ($B)	284	135
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Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

- ETHC over the 20-year time horizon w/o collecting additional information (EV|CI) = **$446 B**

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- ETAP (w/o delay) reduces ETSC by **$297 B**
- THHA (w/o delay) reduces ETSC by **$314 B**

	ETAP	THHA
EV|CI ($B)		446
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	ETAP	**THHA**
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Scenario 5
(Medium μ_{exp} and Medium σ_{exp})

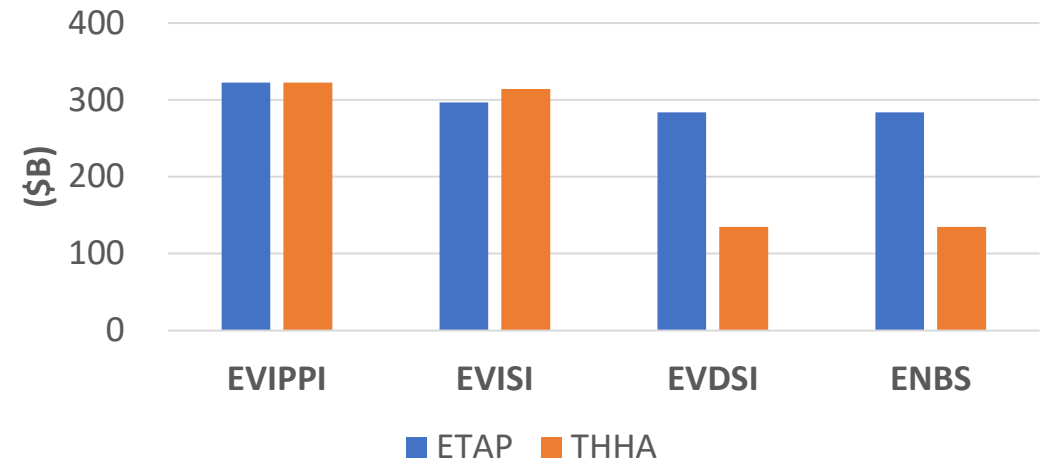- ETHC over the 20-year time horizon w/o collecting additional information (EV|CI) = **$446 B**

- Eliminating uncertainty in μ_{tox} will result in reduction of **$323 B** in ETSC

- ETAP (w/o delay) reduces ETSC by **$297 B**
- THHA (w/o delay) reduces ETSC by **$314 B**

- COD for ETAP (6-months) is **$13 B**
- COD for THHA (8-year) is **$180 B**

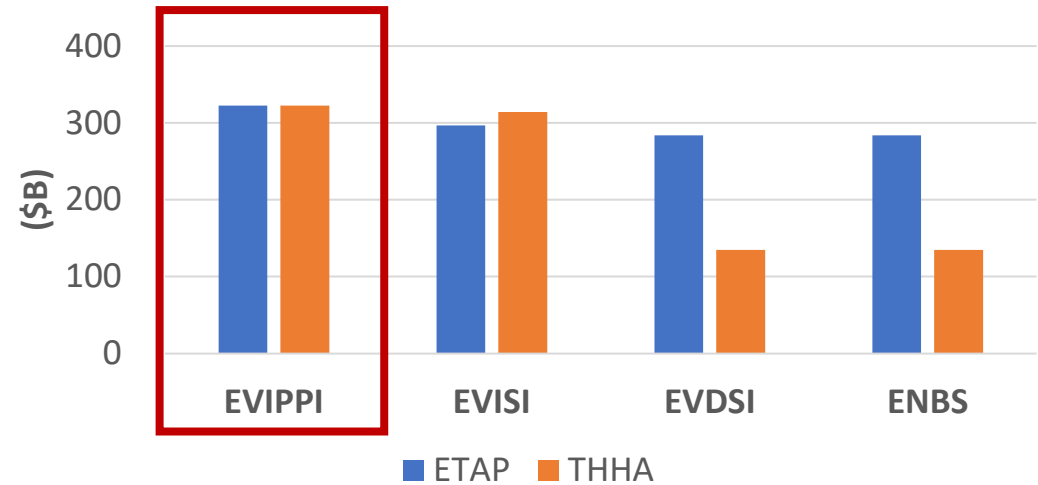|	ETAP	THHA
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(Medium μ_{exp} and Medium σ_{exp})

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- Eliminating uncertainty in μ_{tox} will result in reduction of **$323 B** in ETSC

- ETAP (w/o delay) reduces ETSC by **$297 B**
- THHA (w/o delay) reduces ETSC by **$314 B**

- COD for ETAP (6-months) is **$13 B**
- COD for THHA (8-year) is **$180 B**

- EVDSI and ENBS for ETAP is **$284 B**
- EVDSI and ENBS for THHA is **$135 B**

	ETAP	THHA
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EVIPPI ($B)		323
	ETAP	**THHA**
EVISI ($B)	297	314
COD ($B)	13	180
EVDSI ($B)	284	135
ENBS ($B)	284	135
ROI	1,420,115	33,678

Scenario 5
(Medium $\mu_{\exp}$ and Medium $\sigma_{\exp}$)

- ETHC over the 20-year time horizon w/o collecting additional information (EV|CI) = **$446 B**

- Eliminating uncertainty in μ_{tox} will result in reduction of **$323 B** in ETSC

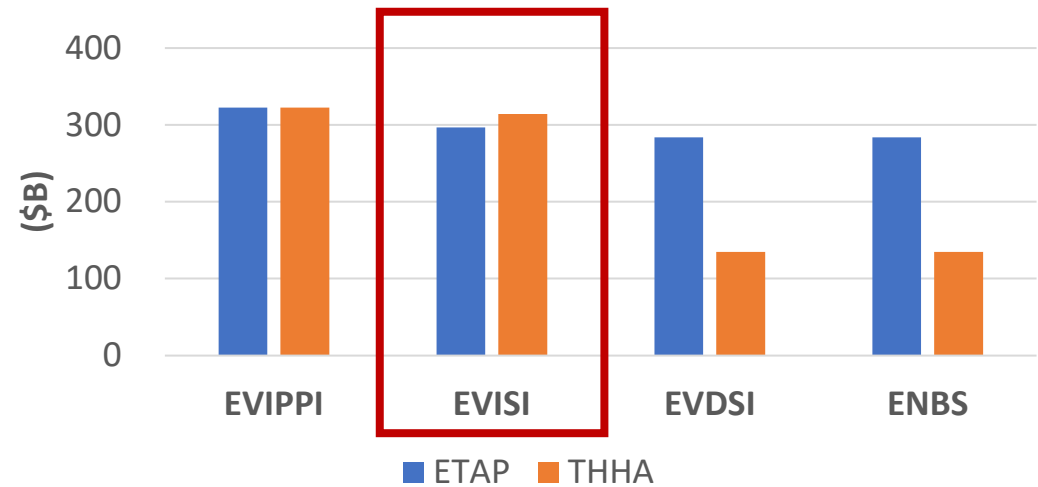- ETAP (w/o delay) reduces ETSC by **$297 B**
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- COD for ETAP (6-months) is **$13 B**
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- EVDSI and ENBS for ETAP is **$284 B**
- EVDSI and ENBS for THHA is **$135 B**

- **ETAP provides greater VOI values** when COD and COT are taken into account

	ETAP	THHA
EV|CI ($B)		446
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	ETAP	**THHA**
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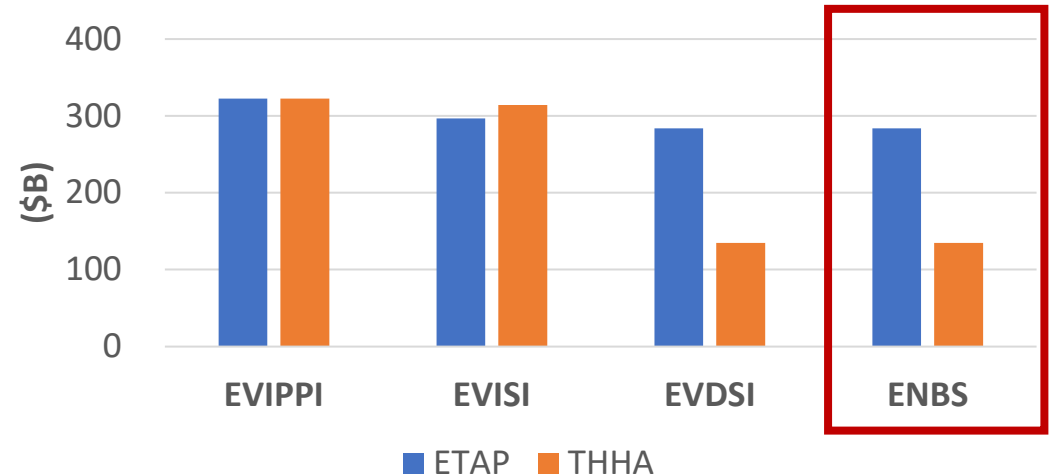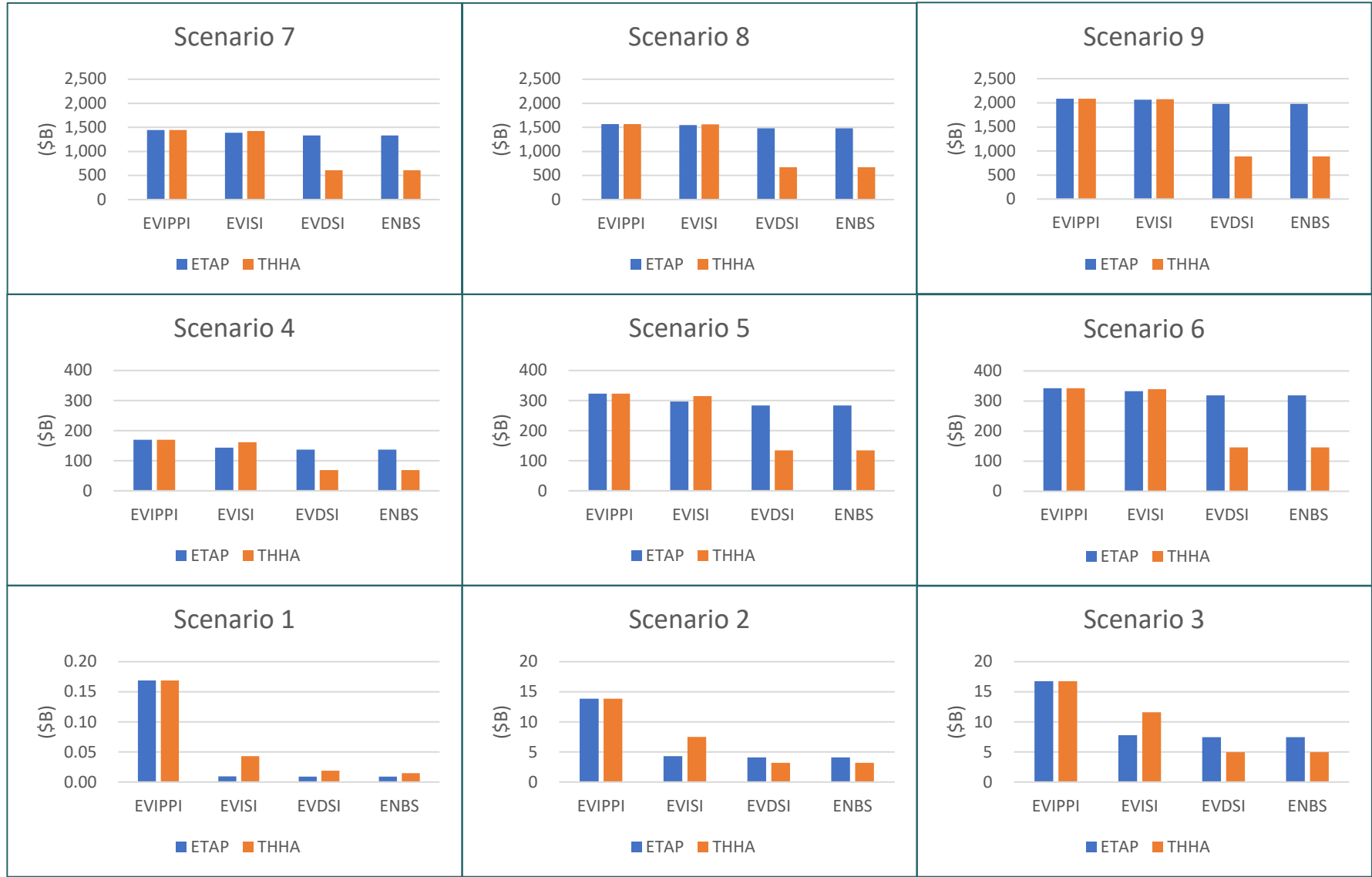
Summary
(TRDM – Baseline Scenarios)

- In scenarios 2 – 9, delay-adjusted VOI metrics prefer ETAP over THHA

- In scenario 1, the EVDSI and ENBS metrics prefer THHA

- A change in μ_{exp} has a greater impact on resulting VOI metrics than a change in σ_{exp}

SENSITIVITY ANALYSIS SCENARIOS
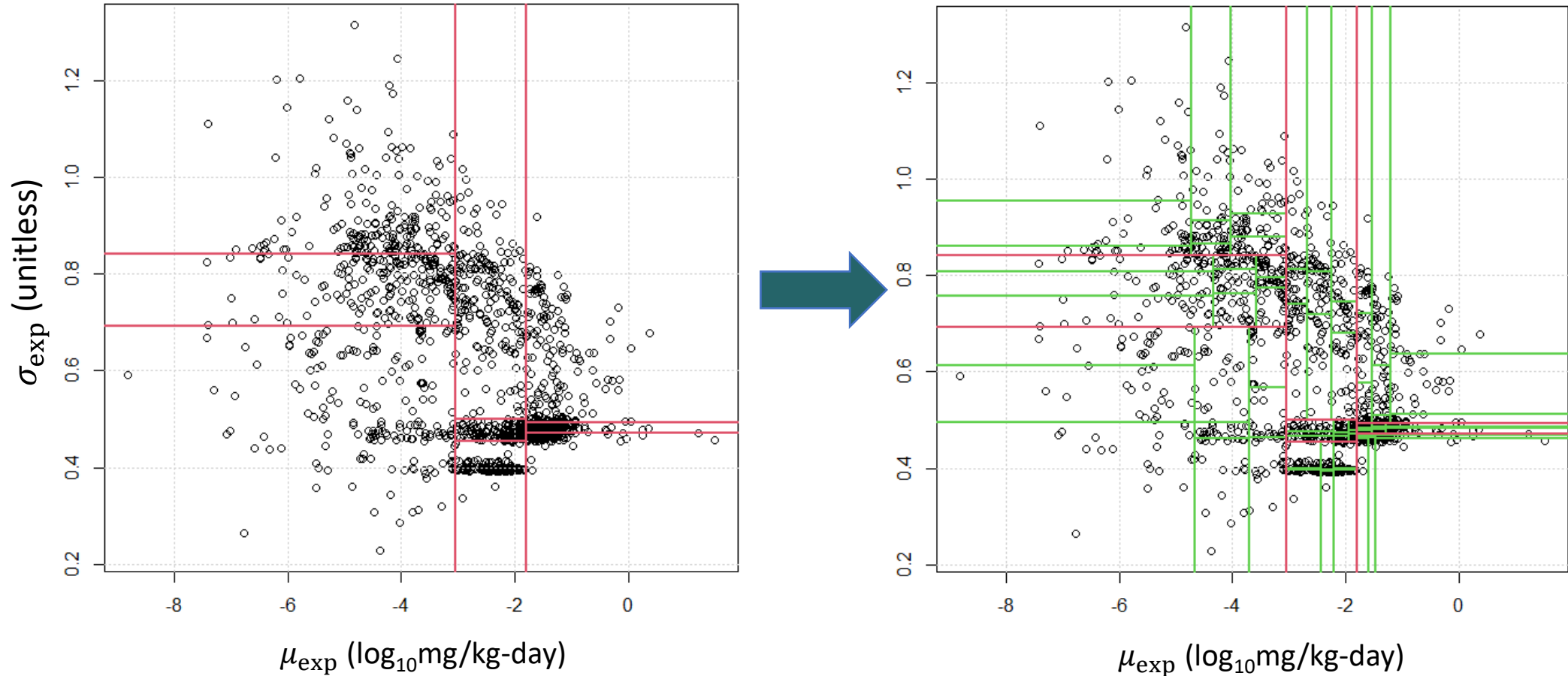
Each of the 9 exposure domains are further partitioned into 3 × 3 sub-domains
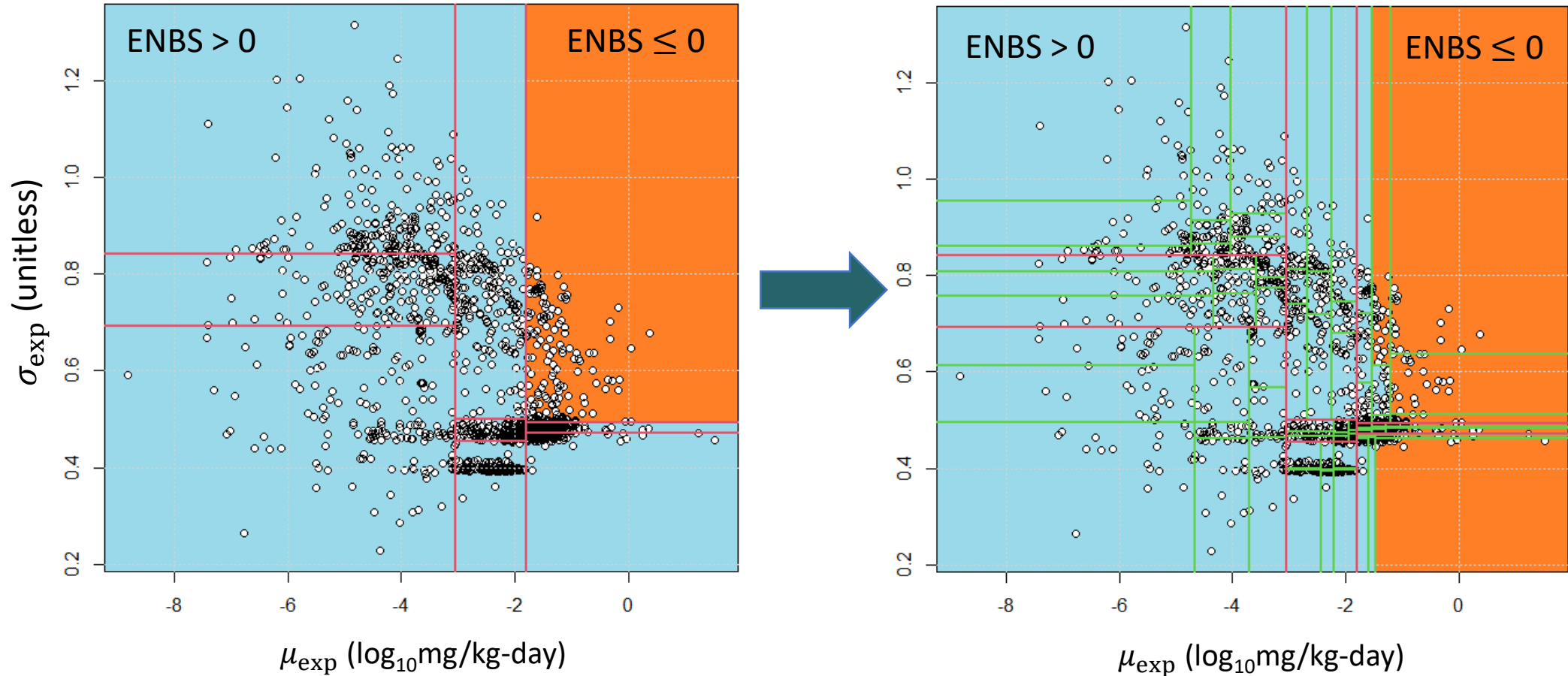
Median exposure (μ_{exp}) has a greater impact on the ENBS than variation in exposure (σ_{exp}) for the BRDM
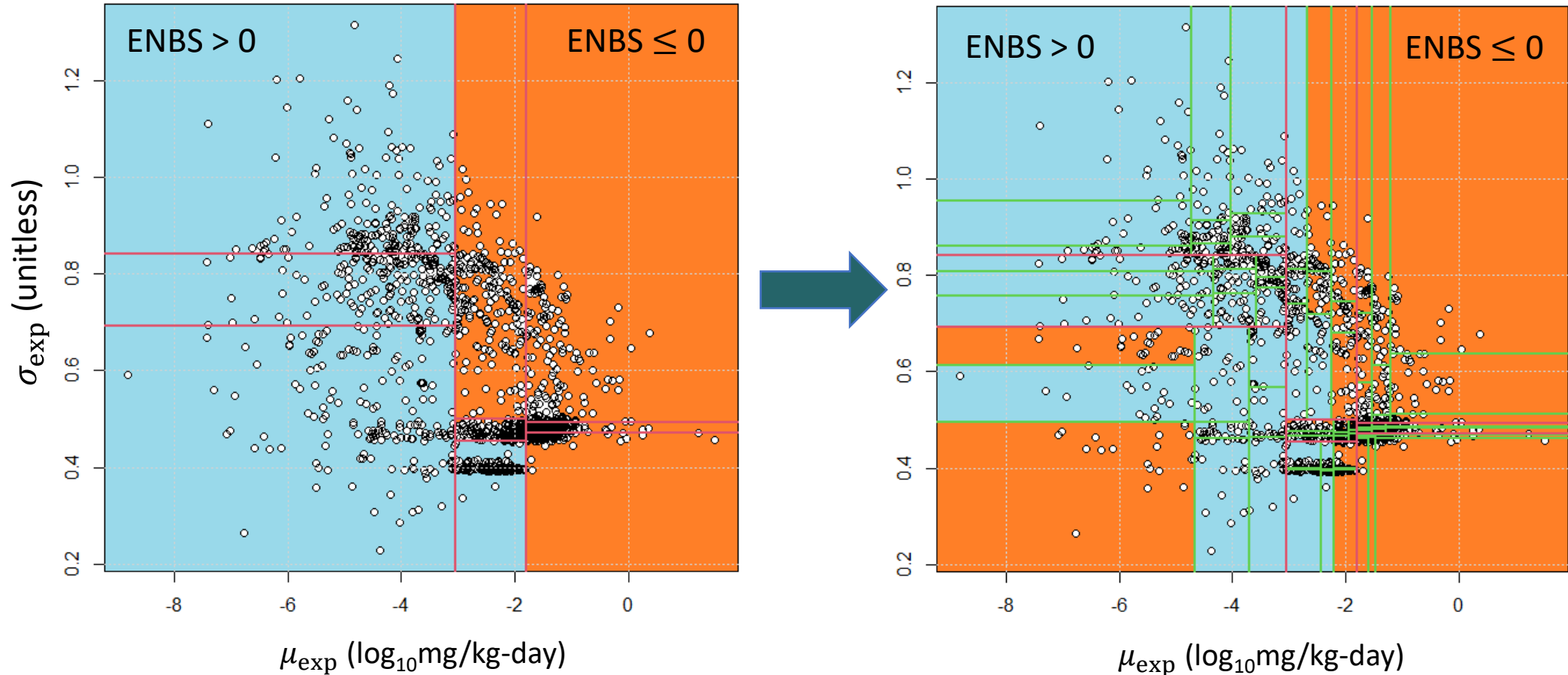
Similar results are observed for THHA, although some negative ENBS values are seen for μ_{exp} and σ_{exp}

Left plot: σ_{exp} (unitless) vs μ_{exp} ($\log_{10}$mg/kg-day). $ENBS_{ETAP} > ENBS_{THHA}$ (blue region, upper). $ENBS_{THHA} > ENBS_{ETAP}$ (pink region, lower left).

Right plot: σ_{exp} (unitless) vs μ_{exp} ($\log_{10}$mg/kg-day). No additional testing required (gray region).
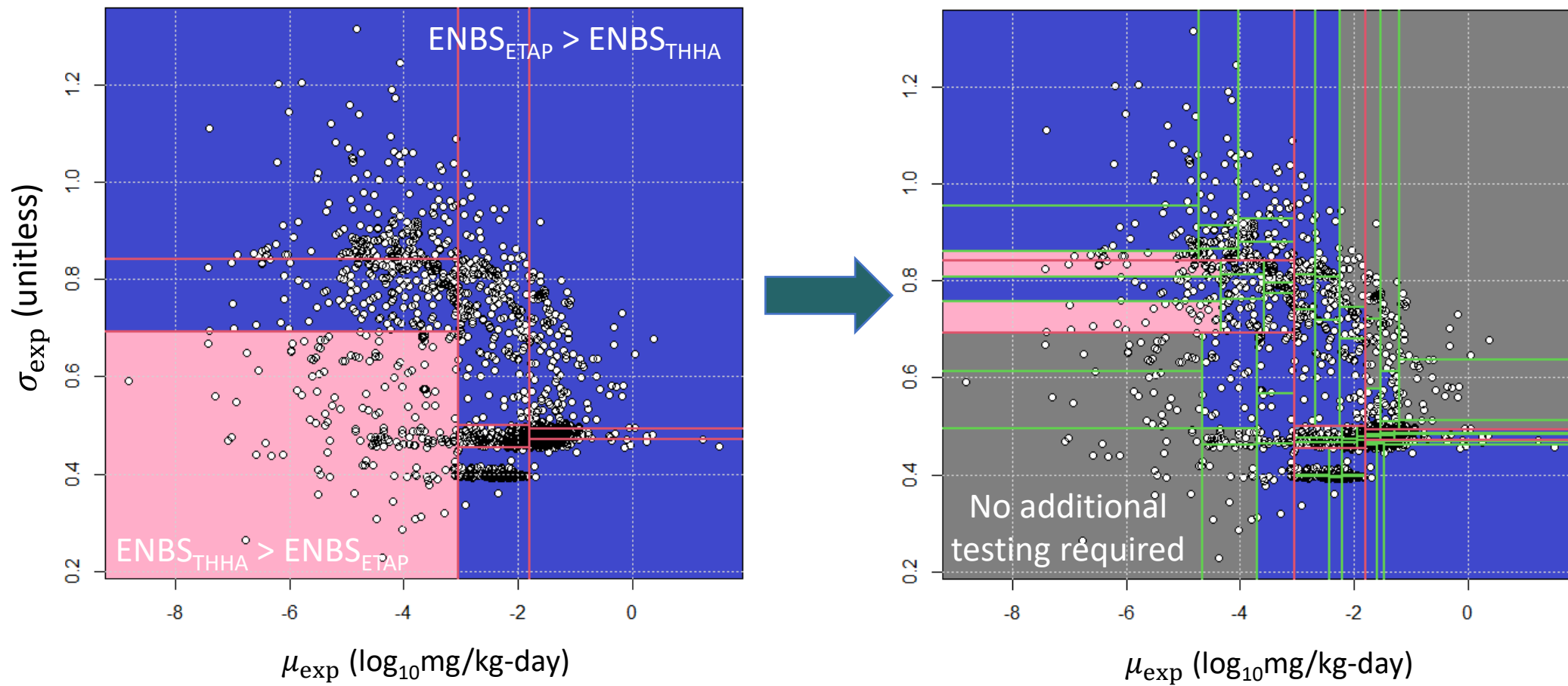
More precise exposure information may lead to regulatory decisions without additional toxicity testing

SA1. Effect of the Quality of Exposure Information

For the BRDM

- ETAP is preferred over THHA in all scenarios, when compared using EVDSI and ENBS

For the TRDM

- More precise exposure information can lead to regulatory decisions without additional toxicity testing in certain cases

- There are 2 scenarios where the ENBS metric prefers THHA, but the ROI metric always prefers ETAP

SA2.1. Effect of the Adverse Health Outcome Cost

- VOI analyses can be conducted for acute, chronic, and fatal outcomes, each of which will have a different economic valuation

- In addition to a notional value of **$10,000 per year** for a chronic adverse health outcome used in the baseline analysis, we use values of **$1,000 per year** and **$110,000 per year** as notional values for acute and fatal outcomes, respectively

SA2.2. Effect of the Cost of Control

- A recent evaluation of the costs of chemical restriction proposals between January 2010 to May 2020 under REACH indicated an annualized total expenditure of €1.7 B across all the proposals (ECHA 2021)

- The mean and median control cost across all chemical control programs included in this program were €53.3 M and €6 M, respectively, corresponding to $50.6 M and $5.7 M, based on average 2022 exchange rates

- ACC_{max} is set to **$578 M** (compared to $23.1 B in the baseline analysis)
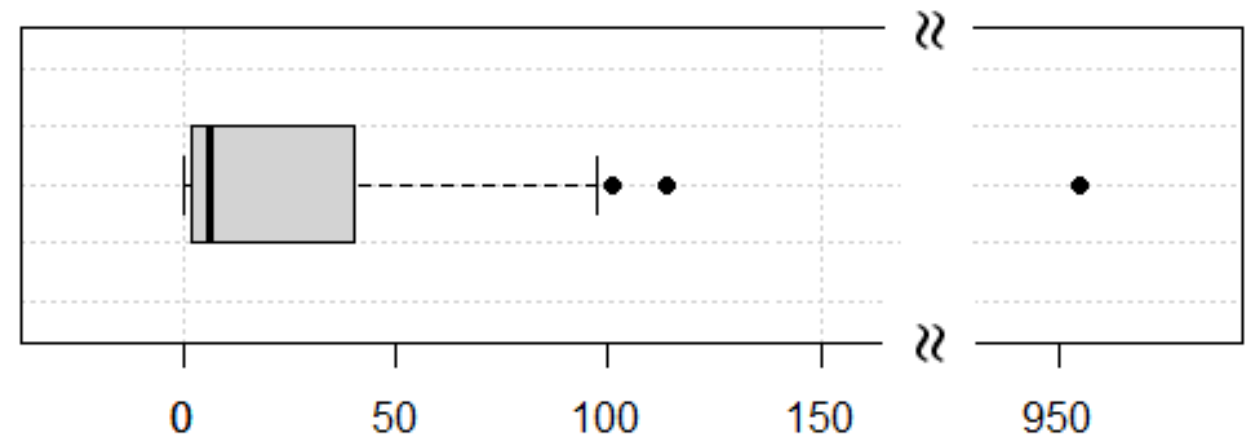
Boxplot of annualized control cost associated with 33 risk management programs under the REACH registration (in €M).

[Based on ECHA (2021). Costs and benefits of REACH restrictions proposed between 2016-2020. ECHA-21-R-02-EN. Helsinki, Finland: European Chemicals Agency.]

ACC: Annualized Control Cost | ECHA: European Chemicals Agency

SA2 – Effect of the Adverse Health Outcome Cost and Cost of Control

Under scenario 5

A. Benefit-risk Decision-making

ACC_{max}	$23.1B (baseline)						$578M	
AHC	$1K		$10K (baseline)		$110K		$10K	
ORE		0		78		100		100
EV|CI ($B)		45		293		1,276		101
EVIPPI ($B)		17		154		150		3
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	12	15	133	143	112	129	2	3
CoD ($B)	1	8	12	169	159	2,147	15	199
EVDSI ($B)	12	6	121	-26	-48	-2,017	-13	-196
ENBS ($B)	12	6	121	-26	-48	-2,017	-13	-196
ROI	59	2	604	-6	-238	-504	-63	-49

B. Target-risk Decision-making

AHC	$1K		$10K (baseline)		$110K	
EV|CI ($B)		45		446		4,903
EVIPPI ($B)		32		323		3,549
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	30	31	297	314	3,263	3,458
CoD ($B)	1	18	13	180	139	1,976
EVDSI ($B)	28	13	284	135	3,124	1,482
ENBS ($B)	28	13	284	135	3,124	1,482
ROI	142	3	1,420	34	15,621	370

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric).
$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

SA2 – Effect of the Adverse Health Outcome Cost and Cost of Control

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Under scenario 5

For the BRDM

- **AHC = $1K** leads to positive delay-adjusted VOI values for THHA

A. Benefit-risk Decision-making

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AHC	$1K		$10K (baseline)		$110K		$10K	
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Under scenario 5

For the BRDM

- **AHC = $1K** leads to positive delay-adjusted VOI values for THHA
- **AHC = $110K** leads to negative VOI values for both ETAP and THHA

SA2 – Effect of the Adverse Health Outcome Cost and Cost of Control

A. Benefit-risk Decision-making

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EVDSI ($B)	12	6	121	-26	-48	-2,017	-13	-196
ENBS ($B)	12	6	121	-26	-48	-2,017	-13	-196
ROI	59	2	604	-6	-238	-504	-63	-49

B. Target-risk Decision-making

AHC	$1K		$10K (baseline)		$110K	
EV|CI ($B)		45		446		4,903
EVIPPI ($B)		32		323		3,549
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	30	31	297	314	3,263	3,458
CoD ($B)	1	18	13	180	139	1,976
EVDSI ($B)	28	13	284	135	3,124	1,482
ENBS ($B)	28	13	284	135	3,124	1,482
ROI	142	3	1,420	34	15,621	370

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric).
$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

Under scenario 5

For the BRDM

- **AHC = $1K** leads to positive delay-adjusted VOI values for THHA
- **AHC = $110K** leads to negative VOI values for both ETAP and THHA
- Reduced ACC_{max} has similar effect to increased AHC

SA2 – Effect of the Adverse Health Outcome Cost and Cost of Control

A. Benefit-risk Decision-making

ACC$_{max}$	$23.1B (baseline)						$578M	
AHC	$1K		$10K (baseline)		$110K		$10K	
ORE		0		78		100		100
EV|CI ($B)		45		293		1,276		101
EVIPPI ($B)		17		154		150		3
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	12	15	133	143	112	129	2	3
CoD ($B)	1	8	12	169	159	2,147	15	199
EVDSI ($B)	12	6	121	-26	-48	-2,017	-13	-196
ENBS ($B)	12	6	121	-26	-48	-2,017	-13	-196
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$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

Under scenario 5

For the BRDM

- **AHC = $1K** leads to positive delay-adjusted VOI values for THHA
- **AHC = $110K** leads to negative VOI values for both ETAP and THHA
- Reduced ACC$_{max}$ has similar effect to increased AHC

For the TRDM

- A change in AHC results in a proportional change in VOI values

SA2 – Effect of the Adverse Health Outcome Cost and Cost of Control

A. Benefit-risk Decision-making

ACC_{max}	$23.1B (baseline)						$578M	
AHC	$1K		$10K (baseline)		$110K		$10K	
ORE		0		78		100		100
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EVIPPI ($B)		17		154		150		3
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Under scenario 5

For the BRDM

- **AHC = $1K** leads to positive delay-adjusted VOI values for THHA
- **AHC = $110K** leads to negative VOI values for both ETAP and THHA
- Reduced ACC_{max} has similar effect to increased AHC

For the TRDM

- A change in AHC results in a proportional change in VOI values

The ETAP is preferred over THHA in all cases using the ENBS metric

SA3 – Effect of the Toxicity Distribution
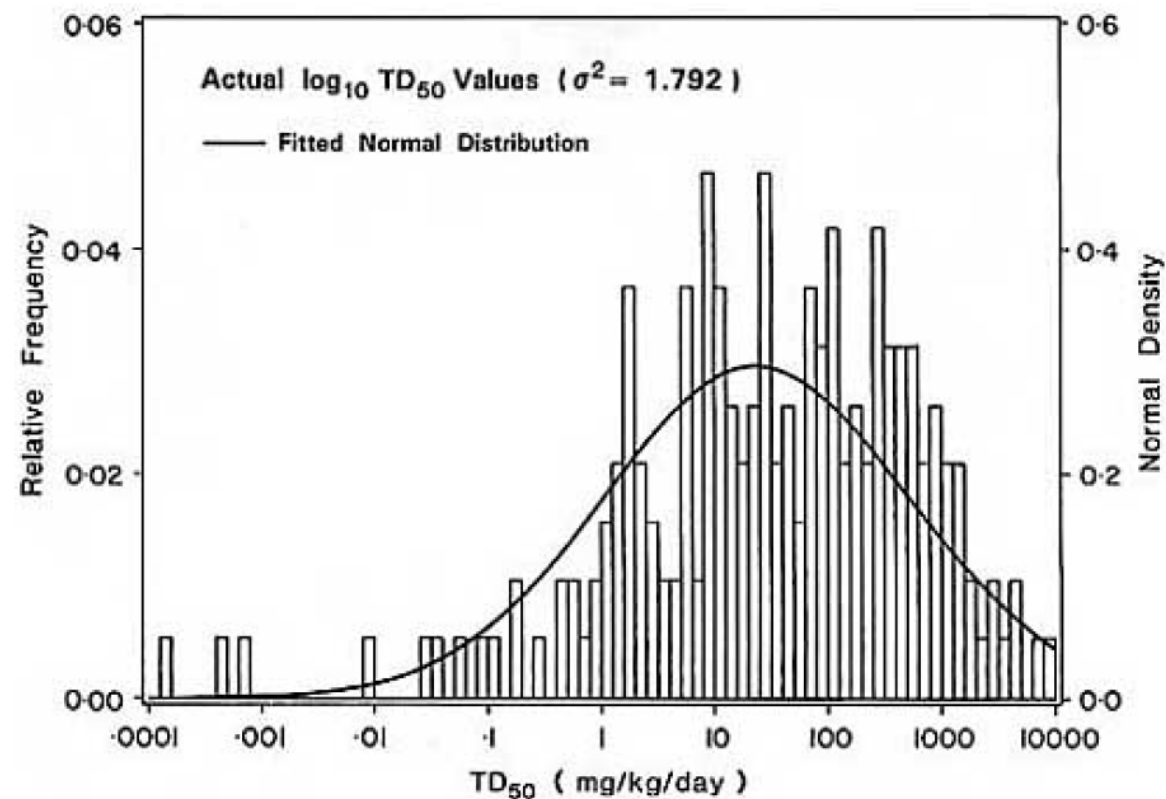
The average HD_M^{50} across 191 carcinogens is approximately **5.0 mg/kg-day**
(greater than **3.3 mg/kg-day** used in the baseline analysis)
Valuation of **$110,000 per year** is used for adverse health outcome

TD_{50}: Dose resulting in 50% tumor response

SA3 – Effect of the Toxicity Distribution

A. Benefit-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
ORE	27		61		48		86		98		100		100		100		100	
EV|CI ($B)	129		238		195		358		572		677		2,329		2,480		3,806	
EVIPPI ($B)	66		116		93		175		180		136		113		118		59	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	56	61	101	108	81	87	156	166	152	165	107	120	74	92	77	96	32	44
CoD ($B)	3	39	7	97	5	67	23	313	51	693	65	875	324	4,349	348	4,671	555	7,443
EVDSI ($B)	54	22	94	11	76	20	133	-147	101	-528	42	-754	-249	-4,258	-270	-4,575	-522	-7,400
ENBS ($B)	54	22	94	11	76	20	133	-147	101	-528	42	-754	-249	-4,258	-270	-4,575	-522	-7,400
ROI	268,774	5,456	469,678	2,631	381,306	5,081	666,416	-36,710	503,453	-132,048	212,002	-188,563	-1,247,370	-1,064,451	-1,350,566	-1,143,794	-2,612,345	-1,849,906

B. Target-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	137		300		224		739		1,620		2,087		9,848		10,557		16,787	
EVIPPI ($B)	0		34		47		545		1,187		1,472		6,928		7,514		11,375	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	0.01	0.04	7	15	15	28	407	491	993	1,126	1,360	1,429	6,389	6,733	7,266	7,430	11,062	11,257
CoD ($B)	0.00	0.02	0	9	1	16	17	280	42	643	58	817	272	3,848	310	4,246	471	6,433
EVDSI ($B)	0.01	0.02	6	7	15	12	390	210	951	482	1,302	612	6,116	2,885	6,957	3,184	10,591	4,824
ENBS ($B)	0.01	0.01	6	7	15	12	390	210	951	482	1,302	612	6,116	2,885	6,957	3,184	10,591	4,824
ROI	25	3	31,761	1,630	72,820	3,038	1,950,546	52,562	4,754,909	120,575	6,512,120	153,093	30,582,137	721,341	34,782,567	795,971	52,952,843	1,205,927

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric).
$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

BRDM: The ETAP was preferred over THHA in all scenarios (EVDSI & ENBS)
BRDM: More scenarios produced negative delay-adjusted VOI values due to increased AHC valuation
TRDM: The ETAP was preferred in 7 scenarios using the ENBS metric

SA4 – Effect of the Affected Population Size

- Baseline analysis assumed 330M people were affected, representing the situation in which essentially 100% of the U.S. population is exposed to the chemical of interest

- Sensitivity analyses were performed with 165M (50%) and 33M (10%) people were exposed

M: Millions of people

SA4 – Effect of the Affected Population Size

Under scenario 5

A. Benefit-risk decision-making

Population size	330M (Baseline)		165M		33M	
ORE	78		49		0	
EV|CI ($B)	293		189		45	
EVIPPI ($B)	154		106		17	
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	133	143	91	98	12	15
CoD ($B)	12	169	5	75	1	8
EVDSI ($B)	121	-26	86	23	12	6
ENBS ($B)	121	-26	86	23	12	6
ROI	603,877	-6,478	429,503	5,761	59,026	1,563

B. Target-risk decision-making

Population size	330M (Baseline)		165M		33M	
EV|CI ($B)	446		223		45	
EVIPPI ($B)	323		161		32	
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	297	314	148	157	30	31
CoD ($B)	13	180	6	90	1	18
EVDSI ($B)	284	135	142	67	28	13
ENBS ($B)	284	135	142	67	28	13
ROI	1,420,115	33,678	710,057	16,839	142,011	3,367

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric).
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$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

Under scenario 5

For the BRDM
- A reduction in population size leads to a significant reduction in the COD

SA4 – Effect of the Affected Population Size

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Population size	330M (Baseline)		165M		33M	
ORE	78		49		0	
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	ETAP	THHA	ETAP	THHA	ETAP	THHA
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Under scenario 5

For the BRDM
- A reduction in population size leads to a significant reduction in the COD

For the TRDM
- A change in the population size results in a proportional change in VOI values

SA4 – Effect of the Affected Population Size

A. Benefit-risk decision-making

Population size	330M (Baseline)		165M		33M	
ORE	78		49		0	
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EVIPPI ($B)	154		106		17	
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	133	143	91	98	12	15
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EVIPPI ($B)	323		161		32	
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Under scenario 5

For the BRDM
- A reduction in population size leads to a significant reduction in the COD

For the TRDM
- A change in the population size results in a proportional change in VOI values

> *The ETAP is preferred over THHA in all scenarios using the delay-adjusted VOI metric*

SA5 – Effect of the Target Risk Level

- In the baseline analysis, the TRDM is concerned about risks that exceed a TRL of 10^{-6}

- The TRL of 10^{-4} is used in the sensitivity analysis, representing the estimated median residual risk associated with non-cancer exposure guideline values reviewed in Chiu et al. (2018)

SA5 – Effect of the Target Risk Level

A. VOI analysis results with TRL of 10^{-6} (Baseline)

10^{-6}

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI ($B)	0.2		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	0.01	0.04	4.3	7.5	7.8	11.6	143	162	297	314	332	339	1,389	1,425	1,545	1,561	2,067	2,078
CoD ($B)	0.00	0.03	0.2	4.3	0.3	6.6	6	92	13	180	14	194	59	814	66	892	88	1,187
EVDSI ($B)	0.01	0.02	4.1	3.2	7.5	5.0	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ENBS ($B)	0.01	0.02	4.1	3.2	7.5	5.0	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ROI	44	4	20,556	801	37,362	1,240	685,100	17,308	1,420,115	33,678	1,590,540	36,319	6,650,803	152,671	7,394,078	167,194	9,895,810	222,597

B. VOI analysis results with TRL of 10^{-4}

10^{-4}

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	NA		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI ($B)	NA		2		3		156		304		317		1,382		1,545		2,035	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	NA	NA	0.2	0.6	0.5	1.2	85	125	199	255	252	288	1,114	1,267	1,359	1,477	1,840	1,945
CoD ($B)	NA	NA	0.0	0.3	0.0	0.7	4	72	8	146	11	164	47	724	58	844	78	1,112
EVDSI ($B)	NA	NA	0.2	0.3	0.5	0.5	82	54	191	109	241	123	1,067	543	1,301	633	1,761	834
ENBS ($B)	NA	NA	0.2	0.3	0.5	0.5	82	54	191	109	241	123	1,067	543	1,301	633	1,761	834
ROI	NA	NA	991	65	2,385	129	407,931	13,412	954,215	27,329	1,206,013	30,800	5,332,748	135,748	6,503,564	158,274	8,806,044	208,416

EVDSI, ENBS, and ROI are shown with color gradation (zero → max , with darker shades of blue indicating larger positive values of the VOI metric).
$B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

VOI results for TRL = 10^{-4} in the sensitivity analysis show a similar pattern (ETAP is preferred over THHA) to those for TRL = 10^{-6} in the baseline analysis

SA6 – Higher Residual Uncertainty in ETAP

- RMSD between 14 BMDs based on ETAP and traditional bioassay is 0.567

- Assigning all of this discordance as a source of uncertainty for the ETAP result leads to an increase in σ_{ETAP} to **0.741** (from 0.442)

- This constitutes a scenario in which ETAP is assumed to have higher residual uncertainty than baseline scenarios

Figure Credit: Logan Everett

A. Benefit-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
ORE	0		0		0		52		78		88		100		100		100	
EV|CI ($B)	35		71		53		187		293		326		683		718		915	
EVIPPI ($B)	10		24		15		113		154		146		119		122		74	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	4	8	13	21	7	12	83	105	112	143	106	135	59	101	59	103	27	59
CoD ($B)	0	5	1	12	0	7	5	85	11	169	12	172	64	876	69	952	99	1,342
EVDSI ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ENBS ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ROI	20,875	856	64,342	2,226	34,941	1,327	389,540	5,046	504,365	-6,478	471,870	-9,124	-23,700	-193,780	-49,121	-212,216	-357,880	-320,868

B. Target-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI ($B)	0		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	0.00	0.04	0.8	7.5	2	12	85	162	227	314	307	339	1,257	1,425	1,466	1,561	2,014	2,078
CoD ($B)	0.00	0.03	0.0	4.3	0	7	4	92	10	180	13	194	54	814	62	892	86	1,187
EVDSI ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ENBS ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ROI	-0.20	3.63	3,826	801	11,068	1,240	408,291	17,308	1,085,604	33,678	1,468,713	36,319	6,019,198	152,671	7,016,162	167,194	9,638,857	222,597

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric). $B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

SA6 – Discordance as an Additional Source of Uncertainty

A. Benefit-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
ORE	0		0		0		52		78		88		100		100		100	
EV|CI ($B)	35		71		53		187		293		326		683		718		915	
EVIPPI ($B)	10		24		15		113		154		146		119		122		74	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	4	8	13	21	7	12	83	105	112	143	106	135	59	101	59	103	27	59
CoD ($B)	0	5	1	12	0	7	5	85	11	169	12	172	64	876	69	952	99	1,342
EVDSI ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ENBS ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ROI	20,875	856	64,342	2,226	34,941	1,327	389,540	5,046	504,365	-6,478	471,870	-9,124	-23,700	-193,780	-49,121	-212,216	-357,880	-320,868

B. Target-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI ($B)	0		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	0.00	0.04	0.8	7.5	2	12	85	162	227	314	307	339	1,257	1,425	1,466	1,561	2,014	2,078
CoD ($B)	0.00	0.03	0.0	4.3	0	7	4	92	10	180	13	194	54	814	62	892	86	1,187
EVDSI ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ENBS ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ROI	-0.20	3.63	3,826	801	11,068	1,240	408,291	17,308	1,085,604	33,678	1,468,713	36,319	6,019,198	152,671	7,016,162	167,194	9,638,857	222,597

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric). $B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

BRDM: The ETAP is still preferred over THHA in all scenarios (EVDSI & ENBS)

SA6 – Discordance as an Additional Source of Uncertainty

A. Benefit-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
ORE	0		0		0		52		78		88		100		100		100	
EV|CI ($B)	35		71		53		187		293		326		683		718		915	
EVIPPI ($B)	10		24		15		113		154		146		119		122		74	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	4	8	13	21	7	12	83	105	112	143	106	135	59	101	59	103	27	59
CoD ($B)	0	5	1	12	0	7	5	85	11	169	12	172	64	876	69	952	99	1,342
EVDSI ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ENBS ($B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283
ROI	20,875	856	64,342	2,226	34,941	1,327	389,540	5,046	504,365	-6,478	471,870	-9,124	-23,700	-193,780	-49,121	-212,216	-357,880	-320,868

B. Target-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
EV|CI ($B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI ($B)	0		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI ($B)	0.00	0.04	0.8	7.5	2	12	85	162	227	314	307	339	1,257	1,425	1,466	1,561	2,014	2,078
CoD ($B)	0.00	0.03	0.0	4.3	0	7	4	92	10	180	13	194	54	814	62	892	86	1,187
EVDSI ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ENBS ($B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890
ROI	-0.20	3.63	3,826	801	11,068	1,240	408,291	17,308	1,085,604	33,678	1,468,713	36,319	6,019,198	152,671	7,016,162	167,194	9,638,857	222,597

EVDSI, ENBS, and ROI are shown with color gradation (min → zero → max , with darker shades of red and blue indicating larger negative and larger positive values, respectively, of the VOI metric). $B, Billions of U.S. dollars; $M, Millions of U.S. dollars; $K, Thousands of U.S. dollars.

BRDM: The ETAP is still preferred over THHA in all scenarios (EVDSI & ENBS)

TRDM: ETAP is preferred over THHA in 6 scenarios (EVDSI & ENBS)

SUMMARY

Summary for the BRDM

Description (Section)	Number of scenarios				
	All	No testing preferred	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.1)	9	1	8	8	8
Exposure sensitivity analysis (6.2.1)	81	10	71	71	71
Cost sensitivity analysis (6.2.2)	27	12	15	15	15
Toxicity sensitivity analysis (6.2.3)	9	3	6	6	6
Population size sensitivity analysis (6.2.4)	18	0	18	18	18
Discordance sensitivity analysis (6.2.6)	9	3	6	6	6
All scenarios	**153**	**29 (19%)**	**124 (81%)**	**124 (81%)**	**124 (81%)**

Summary for the BRDM

Description (Section)	Number of scenarios				
	All	**No testing preferred**	**ETAP preferred (EVDSI)**	**ETAP preferred (ENBS)**	**ETAP preferred (ROI)**
Baseline analysis (6.1.1)	9	1	8	8	8
Exposure sensitivity analysis (6.2.1)	81	10	71	71	71
Cost sensitivity analysis (6.2.2)	27	12	15	15	15
Toxicity sensitivity analysis (6.2.3)	9	3	6	6	6
Population size sensitivity analysis (6.2.4)	18	0	18	18	18
Discordance sensitivity analysis (6.2.6)	9	3	6	6	6
All scenarios	**153**	**29 (19%)**	**124 (81%)**	**124 (81%)**	**124 (81%)**

19% of scenarios led to negative EVDSI, ENBS, and ROI for both ETAP and THHA
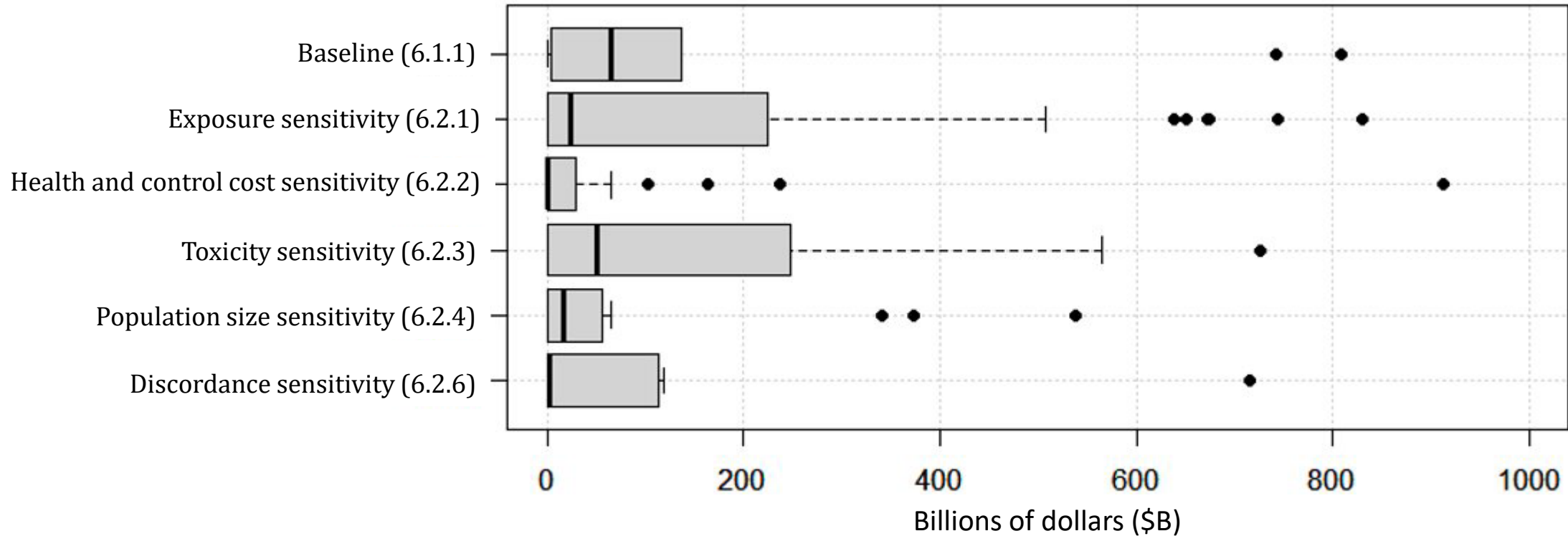
Summary for the BRDM

Description (Section)	Number of scenarios				
	All	No testing preferred	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.1)	9	1	8	8	8
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Toxicity sensitivity analysis (6.2.3)	9	3	6	6	6
Population size sensitivity analysis (6.2.4)	18	0	18	18	18
Discordance sensitivity analysis (6.2.6)	9	3	6	6	6
All scenarios	**153**	**29 (19%)**	**124 (81%)**	**124 (81%)**	**124 (81%)**

19% of scenarios led to negative EVDSI, ENBS, and ROI for both ETAP and THHA
ETAP was preferred over THHA whenever at least one of the tests produced positive delay-adjusted VOI values

Summary for the BRDM

Boxplot of $ENBS_{diff} = ENBS_{ETAP} - ENBS_{THHA}$

*The median difference in ENBS values for ETAP and THHA was **$47 B**, ranging from as low as $4 M to as high as $1 T*

Summary for the TRDM

Description	Number of scenarios				
	All	**No testing required**	**ETAP preferred (EVDSI)**	**ETAP preferred (ENBS)**	**ETAP preferred (ROI)**
Baseline analysis (6.1.2)	9	0	8	8	9
Exposure sensitivity analysis (6.2.1)	81	12	66	66	69
Cost sensitivity analysis (6.2.2)	18	0	16	17	18
Toxicity sensitivity analysis (6.2.3)	9	0	7	7	9
Population size sensitivity analysis (6.2.4)	18	0	16	17	18
TRL sensitivity analysis (6.2.5)	9	1	6	6	8
Discordance sensitivity analysis (6.2.6)	9	0	6	6	8
All scenarios	**153**	**13 (8.5%)**	**125 (89.3%)***	**127 (90.7%)***	**139 (99.3%)***

* Proportions calculated based on 140 (= 153 - 13) scenarios where additional toxicity testing was required

Summary for the TRDM

Description	Number of scenarios				
	All	No testing required	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.2)	9	0	8	8	9
Exposure sensitivity analysis (6.2.1)	81	12	66	66	69
Cost sensitivity analysis (6.2.2)	18	0	16	17	18
Toxicity sensitivity analysis (6.2.3)	9	0	7	7	9
Population size sensitivity analysis (6.2.4)	18	0	16	17	18
TRL sensitivity analysis (6.2.5)	9	1	6	6	8
Discordance sensitivity analysis (6.2.6)	9	0	6	6	8
All scenarios	**153**	**13 (8.5%)**	**125 (89.3%)***	**127 (90.7%)***	**139 (99.3%)***

* Proportions calculated based on 140 (= 153 - 13) scenarios where additional toxicity testing was required

In 13 scenarios, the TRDM required no additional toxicity testing (mostly due to more precise exposure information)

Summary for the TRDM

Description	Number of scenarios				
	All	No testing required	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.2)	9	0	8	8	9
Exposure sensitivity analysis (6.2.1)	81	12	66	66	69
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TRL sensitivity analysis (6.2.5)	9	1	6	6	8
Discordance sensitivity analysis (6.2.6)	9	0	6	6	8
All scenarios	**153**	**13 (8.5%)**	**125 (89.3%)***	**127 (90.7%)***	**139 (99.3%)***

* Proportions calculated based on 140 (= 153 - 13) scenarios where additional toxicity testing was required

In 13 scenarios, the TRDM required no additional toxicity testing (mostly due to more precise exposure information)
When the ENBS metric was used, ETAP was preferred in more than 90% of the scenarios

Summary for the TRDM

Boxplot of $ENBS_{diff} = ENBS_{ETAP} - ENBS_{THHA}$
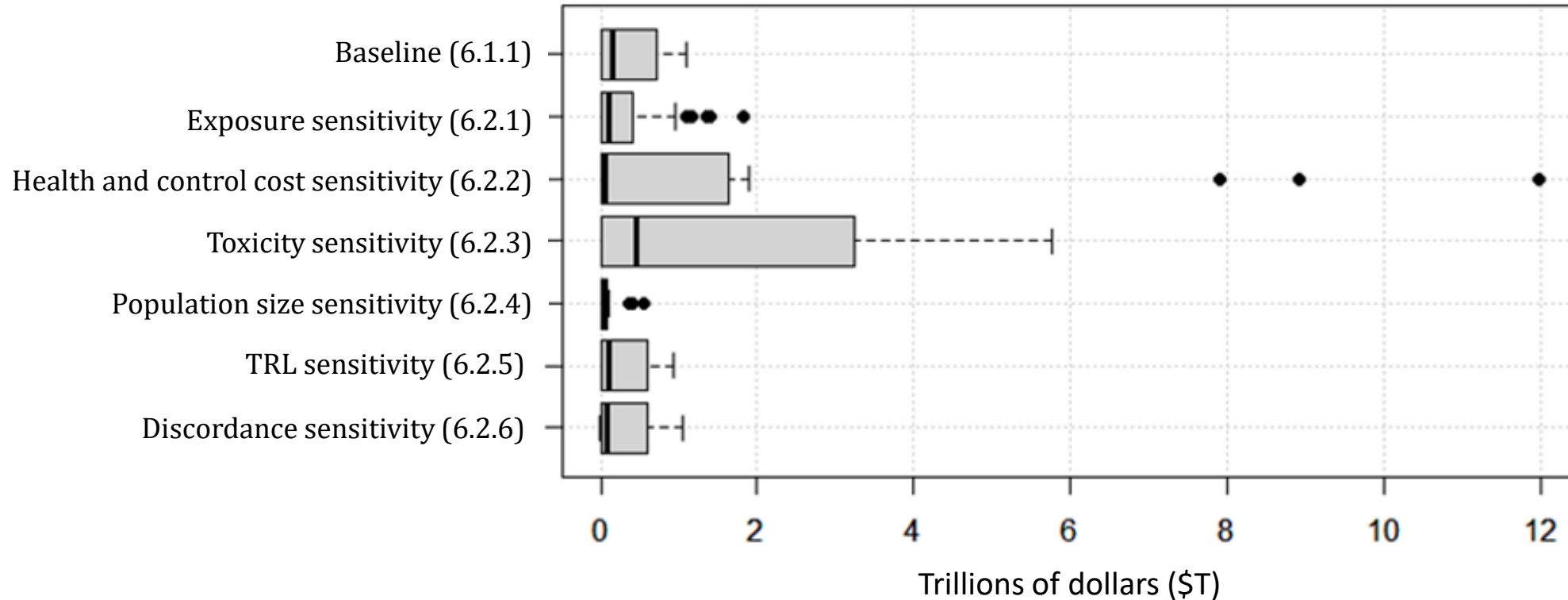
*The median difference in ENBS values for ETAP and THHA was **$81 B**, ranging from as low as −$2.7 M to as high as $12 T*