

Interactive visualization and summarization of toxicology study results across species, routes and durations throughout a drug development program using R Shiny

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Safety of Active Pharmaceutical Ingredient (API)

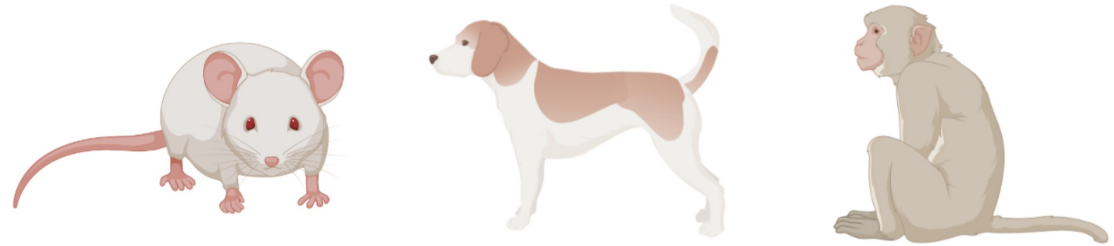
Toxicological Studies in Multiple Species



Multiple Route of Administration



Multiple Duration



- Intravenous, subcutaneous, Oral, Oral Gavage etc.
- Days, Weeks, Months

Metrics for Safety



Safety Margin

Dose Response

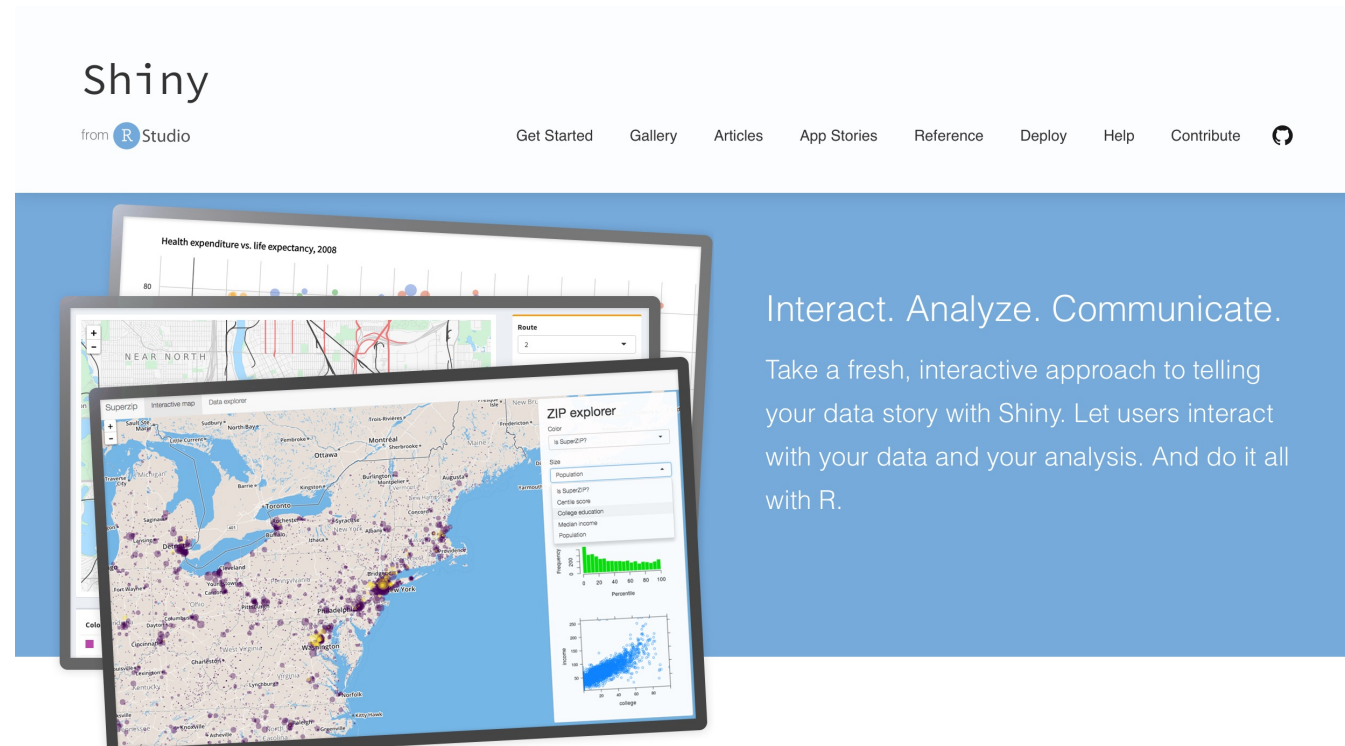
Severity of Findings

Safe or Not Safe?

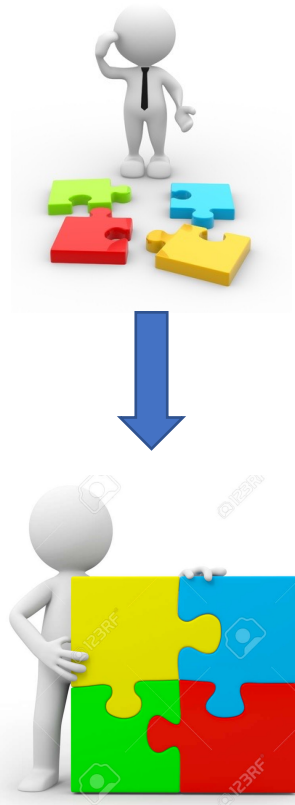
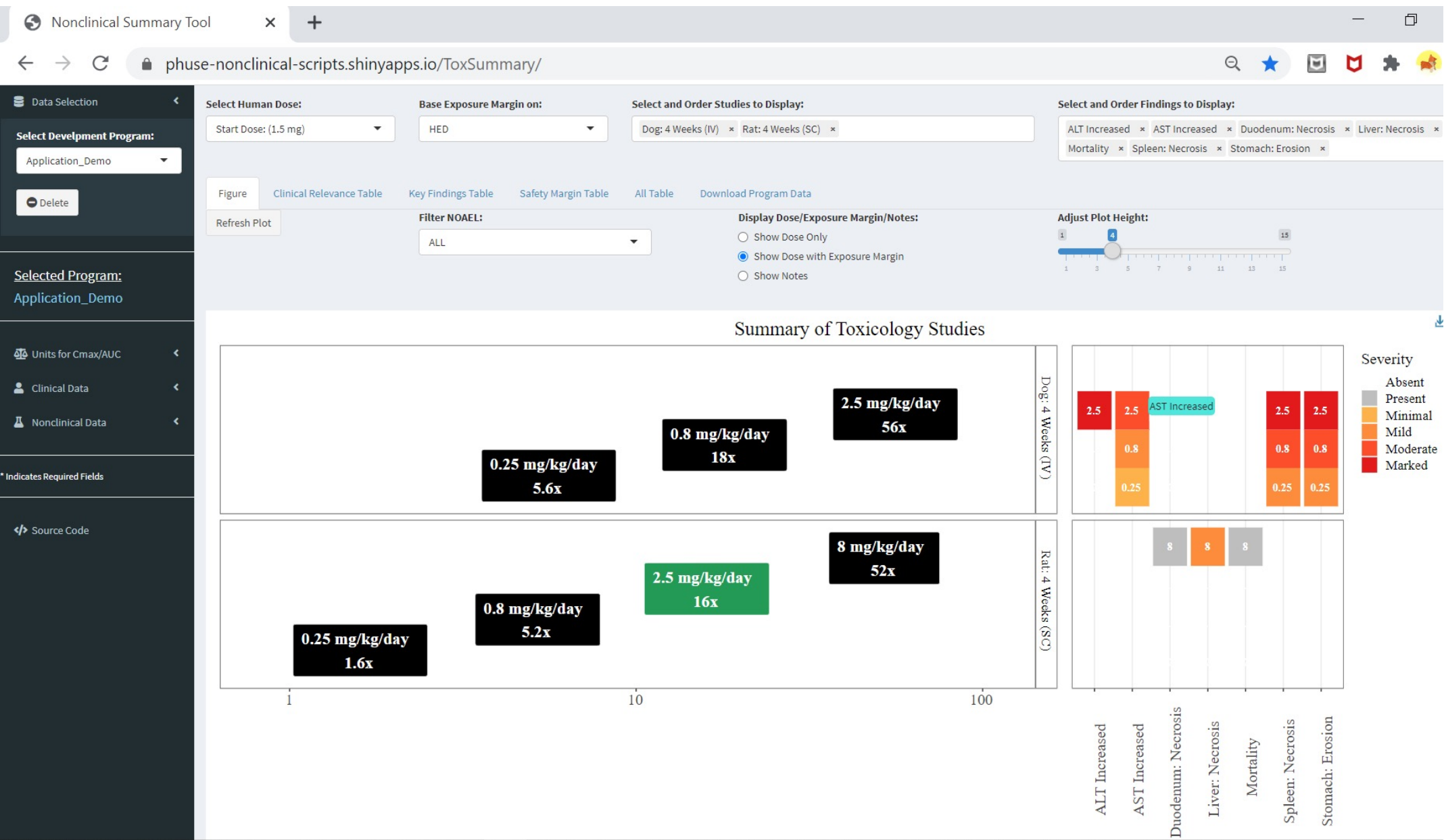


R Shiny for Interactive Visualization

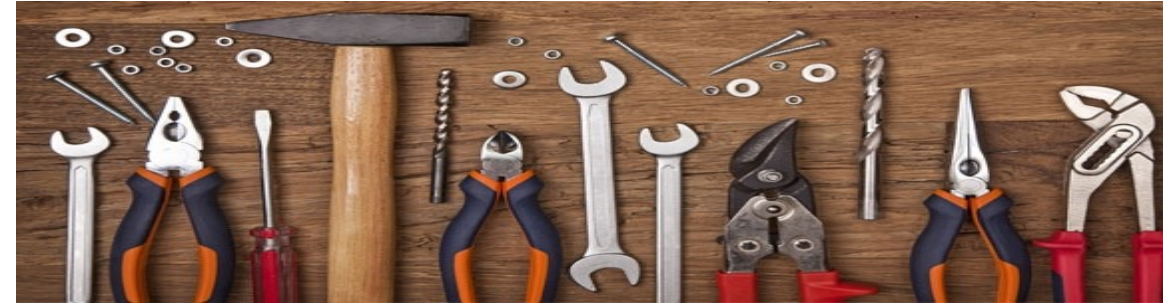
- ❑ Shiny is an R package that allow to create interactive web application using R programming language.
- ❑ The user does not need to be an R programmer to use the application.
- ❑ The user only needs a connection to the server and a modern web browser.



ToxSummary R Shiny Application



Key Functionalities



Select Human Dose:

Start Dose: (1.5 mg) ▼

Base Exposure Margin on:

HED ▼

Select and Order Studies to Display:

Rat: 4 Weeks (SC) × Rat: 13 Weeks (SC) ×
Dog: 4 Weeks (IV) ×
Dog: 13 Weeks with 8 Weeks Recovery (IV) ×
Dog: 39 Weeks with 8 Weeks Recovery (SC) ×
Rat: 13 Weeks with 8 Weeks Recovery (IV) ×

Select and Order Findings to Display:

ALT Increased × AST Increased ×
Duodenum: Congestion ×
Duodenum: Necrosis ×
Liver: Hypertrophy × Liver: Necrosis ×
Mortality × Spleen: Necrosis ×
Spleen: Vacuolation ×
Stomach: Degeneration/regeneration ×
Stomach: Erosion ×

Figure

Clinical Relevance Table

Key Findings Table

Safety Margin Table

All Table

Download Program Data

Refresh Plot

Filter NOAEL:

ALL ▼

Display Dose/Exposure Margin/Notes:

- ☒ Show Dose Only
☐ Show Dose with Exposure Margin
☐ Show Notes

Adjust Plot Height:



Table : **Nonclinical Findings of Potential Clinical Relevance**

Findings	Reversibility	Study	Dose (mg/kg/day)	Clinical Exposure Margin
All	All	All	All	All
ALT Increased	Reversible	Dog: 4 Weeks (IV)	2.5	55.56
		Dog: 39 Weeks with 8 Weeks Recovery (SC)	0.25	5.56
			0.8	17.78
AST Increased	Reversible	Dog: 4 Weeks (IV)	0.25	5.56
			0.8	17.78
			2.5	55.56
	Not Assessed	Rat: 13 Weeks (SC)	0.8	5.16
			2.5	16.13
			8	51.61

Table : Key Study Findings					
Study ▲	NOAEL (mg/kg/day) ▲	Cmax (ng/mL) ▲	AUC (ng*h/mL) ▲	Safety Margin ▲	Findings at Greater than NOAEL for the Study ▲
All	All	All	All	All	All
Rat: 4 Weeks (SC)	2.5	26	99	16.13	Duodenum: Necrosis
					Liver: Necrosis
					Mortality
					Stomach: Degeneration/regeneration
Rat: 13 Weeks (SC)	2.5	108	240	16.13	AST Increased
					Liver: Hypertrophy
					Liver: Necrosis
					Spleen: Necrosis

Table : **Safety Margins Based on NOAEL from Pivotal Toxicology Studies**

Study	NOAEL (mg/kg/day)	HED (mg/day)	Cmax (ng/mL)	AUC (ng*h/mL)	Safety Margin at Starting Dose	Safety Margin at MRHD
All	All	All	All	All	All	All
Rat: 4 Weeks (SC)	2.5	24.19	26	99	16.13	12.1
Rat: 13 Weeks (SC)	2.5	24.19	108	240	16.13	12.1
Dog: 39 Weeks with 8 Weeks Recovery (SC)	0.08	2.67	3	8	1.78	1.33
Rat: 13 Weeks with 8 Weeks Recovery (IV)	0.5	4.84	354	142	3.23	2.42

Click on button below to export the table in a docx file

 Docx file download

Save Your Data

[Figure](#)[Clinical Relevance Table](#)[Key Findings Table](#)[Safety Margin Table](#)[All Table](#)[Download Program Data](#)

Download Program Data in RDS format:

Program Data can be downloaded in RDS format to share with others

Select to Download an Application:

Application_Demo



Download Program Data

Upload Program Data in RDS format:

Upload

Browse...

No file selected

Future Direction

- ❑ Currently, the user needs to enter data manually. We want to create functionality so that the app can read data from the files.
- ❑ This is an open source project that has been shared with industry stakeholders via the PHUSE consortium.
- ❑ A PHUSE project has been proposed to develop practical methods to store and share toxicology study summary information in a machine-readable format for use by applications such as the one presented here.

Where to find the App, Code or Demo?

❑ A publicly accessible version of the application:

<https://phuse-nonclinical-scripts.shinyapps.io/ToxSummary/>

❑ The source code to the public application:

<https://github.com/phuse-org/phuse-scripts/tree/master/contributed/Nonclinical/R/toxSummary>

❑ Demo of the Application on YouTube:

<https://www.youtube.com/watch?v=56V2yxPTWtk>

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