



SENDing Toxicology Study Data Analysis into the 21st Century with a New R Package: sendigR

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SEND: New Opportunities for Cross-Study Analysis of Toxicology Study Data



- In December 2014, the FDA finalized a binding guidance requiring that certain clinical and nonclinical studies be submitted with standardized electronic data, formatted in accordance with the standards recognized in FDA Data Standards Catalog.
 - Study types that are currently modeled in SEND include:
 - Single-Dose General Toxicology
 - Repeat-Dose General Toxicology
 - Carcinogenicity
 - Respiratory and Cardiovascular Safety Pharmacology
 - As of October 2021, > 6,000 SEND datasets have been submitted to CDER.
- The CDISC-SEND data standard has created new opportunities for collaborative development of open-source software solutions to facilitate cross-study analyses of toxicology study data.

FDA/BioCelerate/PHUSE Collaboration



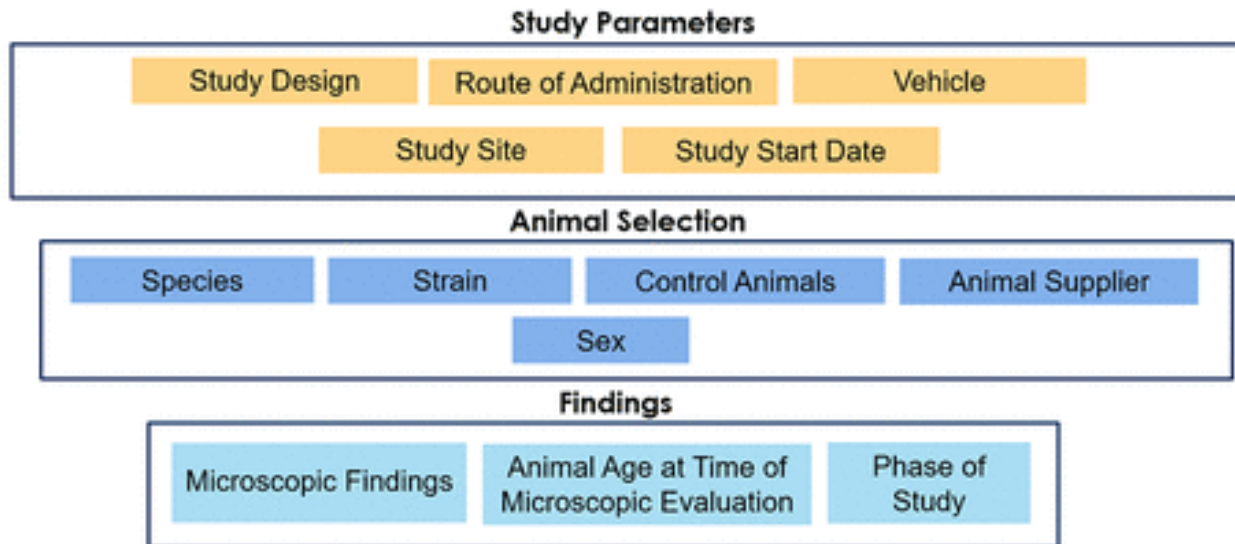
- FDA/CDER has established collaborative partnerships with PHUSE and BioCelerate to develop and publicize novel methods of extracting value from SEND datasets.
- **First publication** focused on identifying challenges and opportunities to improve harmonization of the standard via industry adoption of best practices in SEND dataset creation and/or modification of the SEND data standard in subsequent releases:
 - **SEND harmonization & cross-study analysis: A proposal to better harvest the value from SEND data.** Carfagna MA, Bjerregaard TG, Fukushima T, Houser W, Sloan C, Snyder K, Anderson J, Page T (2020). *Regulatory Toxicology and Pharmacology*, 111, 104542. <https://doi.org/10.1016/j.yrtph.2019.104542>
- **Second publication** explored the feasibility of a practical cross-study analysis use case, i.e., building and querying a historical control database from SEND datasets:
 - **Leveraging the value of CDISC SEND datasets for cross-study analysis: Incidence of microscopic findings in control animals.** Carfagna MA, Anderson J, Eley C, Fukushima T, Horvath J, Houser W, Larsen B, Page T, Russo D, Sloan C, Snyder K, Thompson R, Ullmann G, Whittaker M (2020). *Chemical Research in Toxicology*, 34(2):483-494. <https://doi.org/10.1021/acs.chemrestox.0c00317>

Historical Control Query Design

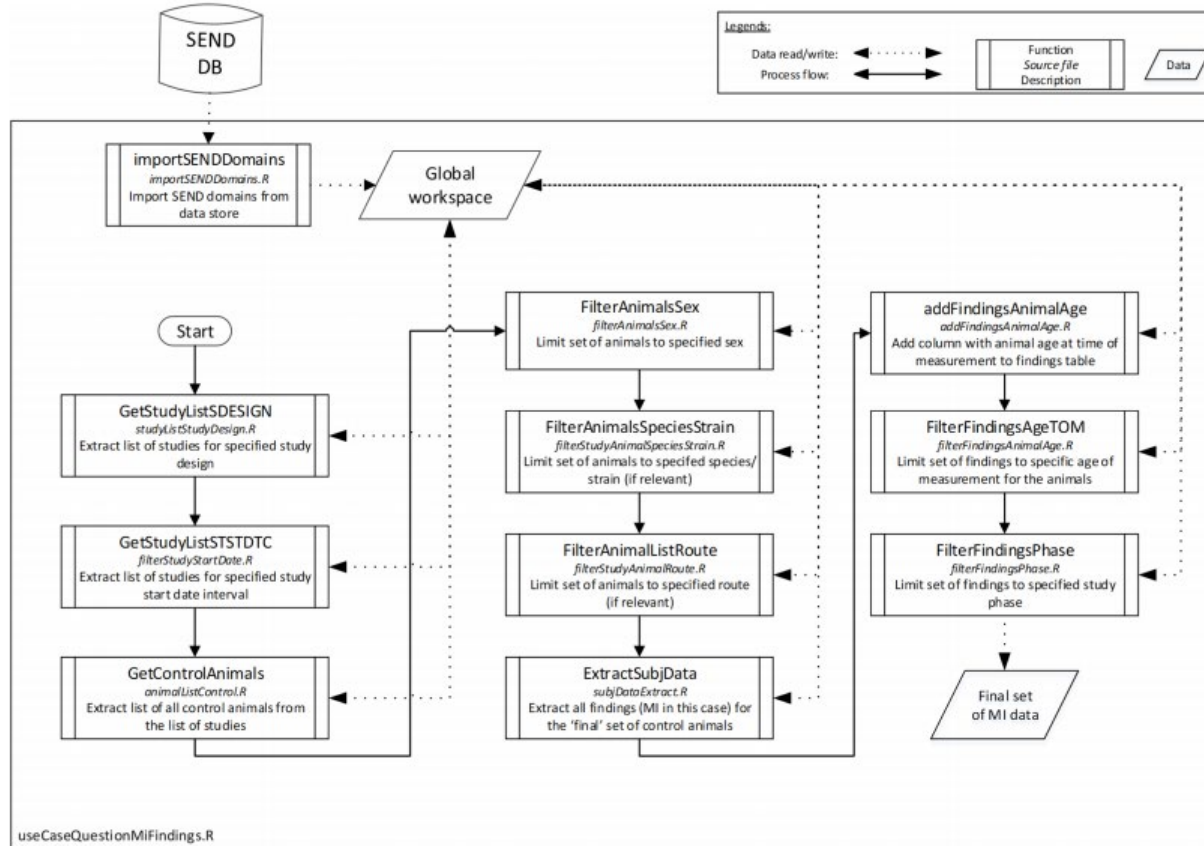


Control Data to Guide Cross Study Analysis Algorithm Development

What are the most common microscopic findings in male beagle dogs 12-18 months of age that were dosed by oral gavage?



Technical Query Design



Query Result



Organ (MISPEC)	Microscopic Finding (MISTRESC)	Incidence ^a
TESTIS	MATURE	45%
GLAND, PITUITARY	CYST	33%
KIDNEY	MINERALIZATION	23%
THYMUS	ATROPHY	12%
GLAND, PARATHYROID	CYST	9%
TESTIS	HYPOPLASIA	9%
TESTIS	HYPOSPERMATOGENESIS	9%
LUNG	INFILTRATE	8%
THYMUS	CYST	8%
EPIDIDYMIS	CELL DEBRIS	6%

^aIncidence is reported as the frequency of the finding per total animals (i.e., 102 male dogs).

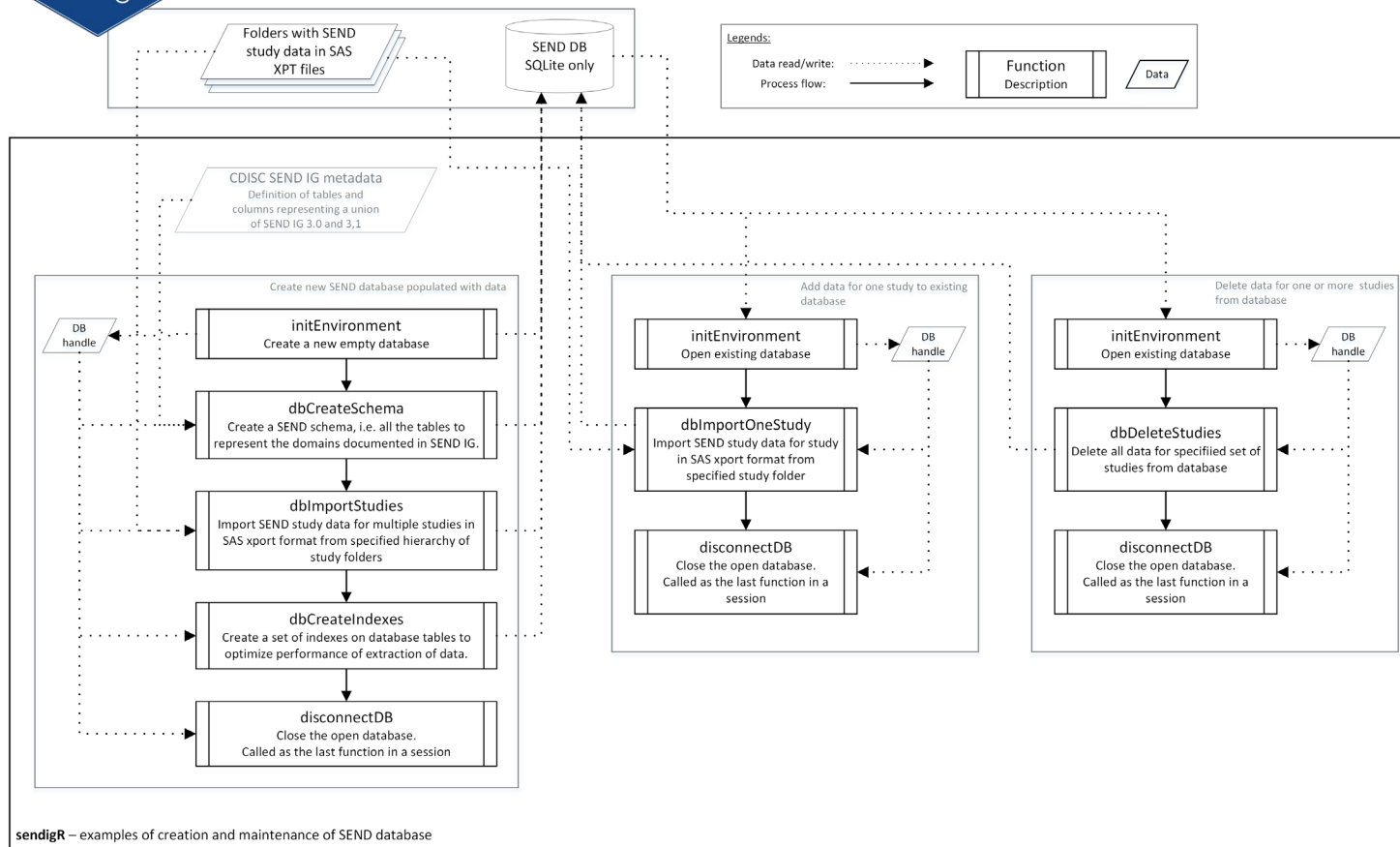


R Package: sendigR

- R scripts from Carfagna et al., 2020 were subsequently enhanced and refactored as an R package called sendigR.
- Functionality of the package is primarily focused on facilitating the targeted extraction of historical control data based on user-specified study and/or animal parameters, e.g. date of study, route of administration of test article, species, animal age, etc.
- Additional functionality will be added to allow users to compare and contrast toxicological profiles of various test articles across studies.
- Source code for sendigR is currently available as a PHUSE GitHub repository:
 - <https://github.com/phuse-org/sendigR>



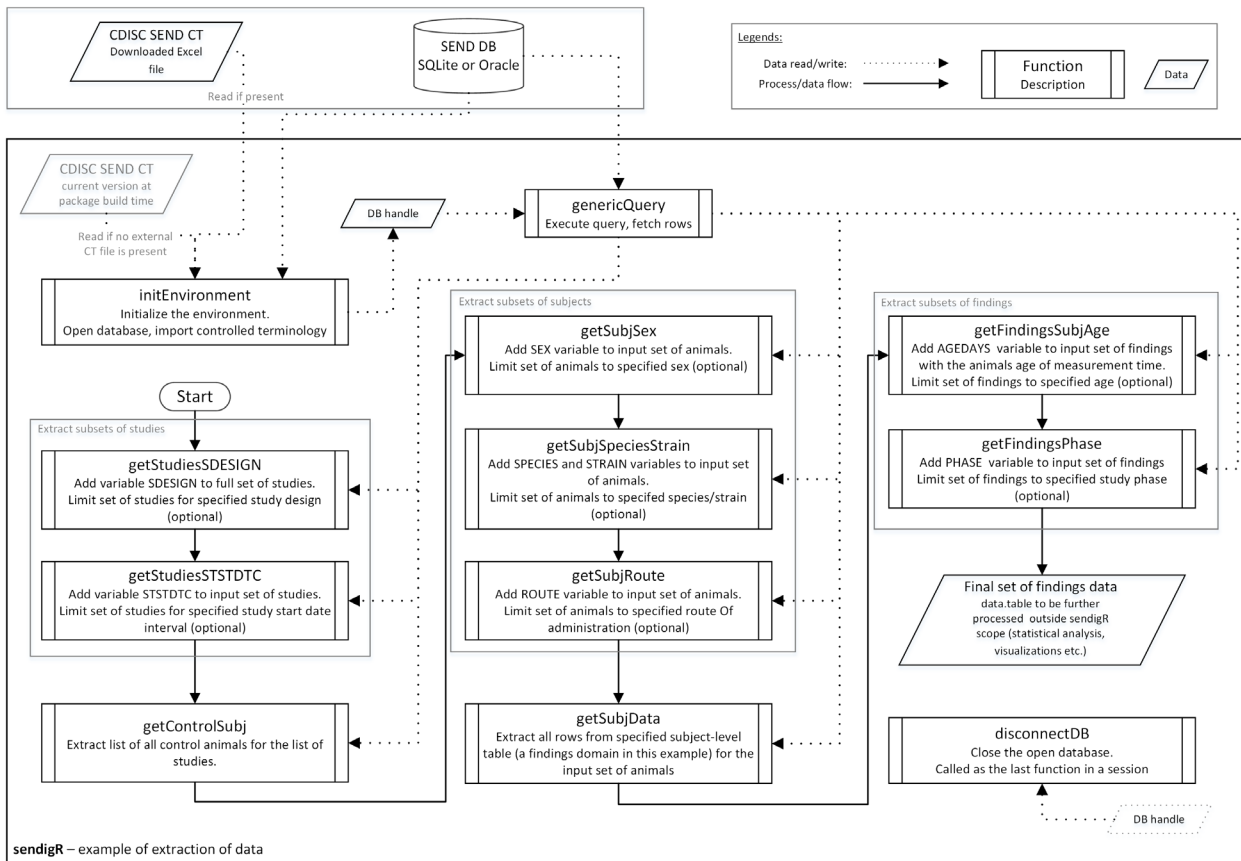
Usage of sendigR to Build/Maintain a Database



Functions in the sendigR package can be used to generate a new SQLite database and add/remove studies from an existing SQLite or Oracle database.



Usage of sendigR to Query a Database



Functions in the sendigR package can be used to query a database of SEND data to extract findings from control animals that match specific criteria.

R Shiny Web Application

- Users who are not familiar with the R programming language are able to utilize the R Shiny web application to perform cross-study analysis.
- Shiny is an R package developed by RStudio to enable R programmers to easily build interactive web applications (<https://shiny.rstudio.com>).
- The R Shiny web application is currently hosted on a public R Shiny server provided by Rstudio:
 - <https://phuse-org.shinyapps.io/sendigR>



R Shiny Web Application

Choose Parameters:

Generate/Update Data

Select Study Start Date Range:

2007-06-04
to
2021-08-19

Select Study Design:

PARALLEL

Select Route of Administration:

ORAL GAVAGE

Select Species:

RAT

Select Strain:

SPRAGUE-DAWLEY

Select Sex:

M

☐ Include uncertain rows

Generate/Update Data

- Users can customize the selection of control animals by study design/date, route of administration, species, strain, and sex.
- Line listings are generated describing the characteristics of each control animal selected.
- Historical control distributions of toxicology study endpoints, i.e. histopathology (MI), clinical pathology (LB), and body weights (BW), are aggregated and displayed in an interactive table.

R Shiny Web Application



Choose Parameters:

Generate/Update Data

Select Study Start Date Range:

2007-06-04 to 2021-08-19

Select Study Design:

PARALLEL

Select Route of Administration:

ORAL GAVAGE

Select Species:

RAT

Select Strain:

SPRAGUE-DAWLEY

Select Sex:

M

☐ Include uncertain rows

Generate/Update Data

ANIMALS MI LB BW Download

Show 10 entries Search:

Table : Filtered Control Animal

	STUDYID	SDESIGN	STSTDTC	TCNTRL	USUBJID	RFSTDTC	AGEDAYS	SEX	SPECIES	STRAIN	ROUTE
	All	All	All	All	All	All	All	All	All	All	All
1	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M01	2016-12-07	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
2	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M02	2016-12-07	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
3	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M03	2016-12-08	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
4	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M04	2016-12-08	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
5	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M05	2016-12-09	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
6	CJ16050	PARALLEL	2016-11-28	Vehicle Control	CJ16050_00M06	2016-12-09	56	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
7	GLP003	PARALLEL	2007-06-04	Vehicle Control	107001349	2007-06-12	64	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
8	GLP003	PARALLEL	2007-06-04	Negative Control	107001351	2007-06-12	64	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
9	GLP003	PARALLEL	2007-06-04	Vehicle Control	107001358	2007-06-12	64	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE
10	GLP003	PARALLEL	2007-06-04	Vehicle Control	107001360	2007-06-12	64	M	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE

Showing 1 to 10 of 69 entries CSV Excel Copy PDF

Previous 1 2 3 4 5 6 7 Next

R Shiny Web Application

Choose Parameters:

Generate/Update Data

Select Study Start Date Range:
 to

Select Study Design:

Select Route of Administration:

Select Species:

Select Strain:

Select Sex:

☐ Include uncertain rows

Generate/Update Data

[ANIMALS](#)
[MI](#)
[LB](#)
[BW](#)
[Download](#)


[MI Findings](#)
[Individual Records](#)
[Aggregate Table](#)

Show entries Search:

	MISPEC	SPECIES	STRAIN	SEX	ROUTE	MISTRESC	N	Incidence
	["KIDNEY"]	All	All	All	All	All	All	All
50	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	NORMAL	12	40.00%
44	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	BASOPHILIC TUBULES	7	23.33%
49	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	NEPHROPATHY	6	20.00%
51	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	VACUOLATION	4	13.33%
47	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	INFLAMMATION	2	6.67%
45	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	CYST	1	3.33%
46	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	INFILTRATION	1	3.33%
48	KIDNEY	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	LYMPHOMA, MALIGNANT	1	3.33%

Showing 1 to 8 of 8 entries (filtered from 103 total entries) Previous Next

R Shiny Web Application

 Choose Parameters: <

Generate/Update Data

Select Study Start Date Range:

2007-06-04

to

2021-08-19

Select Study Design:

PARALLEL

▼

Select Route of Administration:

ORAL GAVAGE ✕

Select Species:

RAT ✕

Select Strain:

SPRAGUE-DAWLEY ✕

Select Sex:

M

▼

☐ Include uncertain rows

Generate/Update Data

ANIMALS

MI

LB

BW

Download

Individual Records

Aggregate Table

Show 25 entries
Search:

	LBSPEC	SPECIES	STRAIN	SEX	ROUTE	LBTESTCD	LBTEST	Mean_LBSTRESN	SD_LBSTRESN	LBSTRESU	N
						[All	All	All	[
7	SERUM	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	ALP	Alkaline Phosphatase	123.09	26.01	U/L	54
8	SERUM	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	ALT	Alanine Aminotransferase	36.76	11.01	U/L	54
9	SERUM	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	AST	Aspartate Aminotransferase	103.59	20.20	U/L	54
11	SERUM	RAT	SPRAGUE-DAWLEY	M	ORAL GAVAGE	BILI	Bilirubin	0.12	0.04	mg/dL	54

Showing 1 to 4 of 4 entries (filtered from 97 total entries)
Previous 1 Next

R Shiny Web Application

Choose Parameters: <

Generate/Update Data

Select Study Start Date Range:

2007-06-04 to 2021-08-19

Select Study Design:

PARALLEL

Select Route of Administration:

ORAL GAVAGE

Select Species:

RAT

Select Strain:

SPRAGUE-DAWLEY

Select Sex:

M

☐ Include uncertain rows

Generate/Update Data

ANIMALS MI LB BW Download

Individual Records Aggregate Table

Show 25 entries Search:

	AGEDAYS	SPECIES	STRAIN	ROUTE	SEX	Mean_BWSTRESN	SD_BWSTRESN	BWORRESU	N
	All	All	All	All	All	All	All	All	All
1	46	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	336.27	11.34	g	15
2	53	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	364.07	16.12	g	15
3	60	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	301.21	57.88	g	63
4	63	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	295.42	8.43	g	48
5	64	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	302.40	9.48	g	48
6	67	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	441.53	15.24	g	15
7	71	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	343.87	16.08	g	47
8	74	RAT	SPRAGUE-DAWLEY	ORAL GAVAGE	M	479.13	24.46	g	15



Conclusion



- The **sendigR** package is a free open-source software solution that will enable data scientists and toxicologists to interrogate large repositories of SEND-formatted toxicology study data.
- Current functionality facilitates historical control data analysis, but functionality will be expanded to cover additional cross-study analysis use cases, e.g., assessment of toxicological profiles, off-target toxicity, etc.
- This is an open, collaborative project. Feel free to try out **sendigR** and contact Kevin.Snyder@fda.hhs.gov if you are interested in providing constructive feedback or getting involved as a contributor.



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