BMD Version Control Meeting

08-11-2024

Opening remarks from CLE

- Thank you for taking the time to meet us
- We do appreciate that EFSA develops tools – good tools help with consistency
- We are here to present Industry's perspective on the BMD tool, as well as describe the issues encountered

CropLife EUROPE

Workflow for BMD in Industry

Introduction

- Today's discussion will focus exclusively on wildlife, not human toxicology
- Our commitment is to make this a success

- The accurate BMD estimation is the pillar to:
  - Set EU agreed B&M toxicity endpoints for the tier I risk assessment
  - Develop higher-tier strategies for Birds and Mammals
  - Finalise the GAP

What regulatory steps does industry undertake to generate B&M data for an EU submission, and how is BMD calculation integrated into this process?

B&M Regulatory submission process

-3 years

-2 years

1. Complete GLP studies – both mammalian tox and avian ecotox. Finalise the proposed GAP
2. Review bird and mammal studies, **calculate BMD for ALL relevant endpoints.** Contract out work (studies review and BMD modeling) if internal resources are not sufficient to support
3. Run tier I risk assessments
4. <u>If tier I risk assessment fails</u>: **Adjust the GAP**
5. <u>If tier I risk assessment fails</u>: Plan for higher tier testing

B&M Regulatory submission process

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-2 years

1. Re-run BMD calculations to check if BMDs are still the same
2. If BMD10s changed, repeat steps 3 and 4 from year -3 !!
3. Run relevant higher tier studies (FS), and plan higher tier studies for next year

-1 years

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B&M Regulatory submission process

-3 years

3. Run tier I risk assessments
4. If tier I risk assessment triggered: **Adjust the GAP**

-2 years

1. Run higher tier studies (FS), and plan higher tier studies for next year

-2 years

1. **Re-run BMD calculations to check if BMDs are still the same**
2. **If BMD10s changed, repeat steps 3 and 4 from year -3**
3. Run higher tier studies (FS), and plan higher tier studies for next year

-1 years

1. Run relevant higher tier studies (PD, PT)
2. Pre-submission meeting with RMS and adjust strategy if needed **!BMD discussion!**

-1 years

1. **Repeat steps 1., 2. from year -2 (see also year -1)**
2. Run relevant higher tier studies (PD, PT)
3. Pre-submission meeting with RMS and adjust strategy if needed **!BMD discussion!**

0 years

B&M Regulatory submission process

RMS/EFSA

1. Review studies, and calculate BMD10 for relevant endpoints
2. Run tier 1 risk assessments

0 years | **+1 years** | **+2 years** | **+3 years**

Compile information, write & submit dossier

RMS/EFSA

1. **Review studies, and calculate BMD10 for relevant endpoints**
2. **Run tier 1 risk assessments**

Conclusions – no version control

Consequences:

- **GAPs may need to be adapted regularly**
- **Significant higher workload expected for both authorities and industry**
- **Significant additional resources needed**
- **Predictability of requirements for higher tier refinements is affected. Higher tier strategy may need to be adapted even after submission**
- **High potential for unharmonised approaches**

No regulated version control: Procedural challenge for all stakeholders

A reliable, robust and stable regulatory version is urgently needed

A mutually agreed solution is needed → let's discuss how we can get there

Case Studies

Case Studies

1. New Version New Results
2. Are the Results Reliable?
3. Practical Issues
4. Understanding the Different Versions

Case Studies

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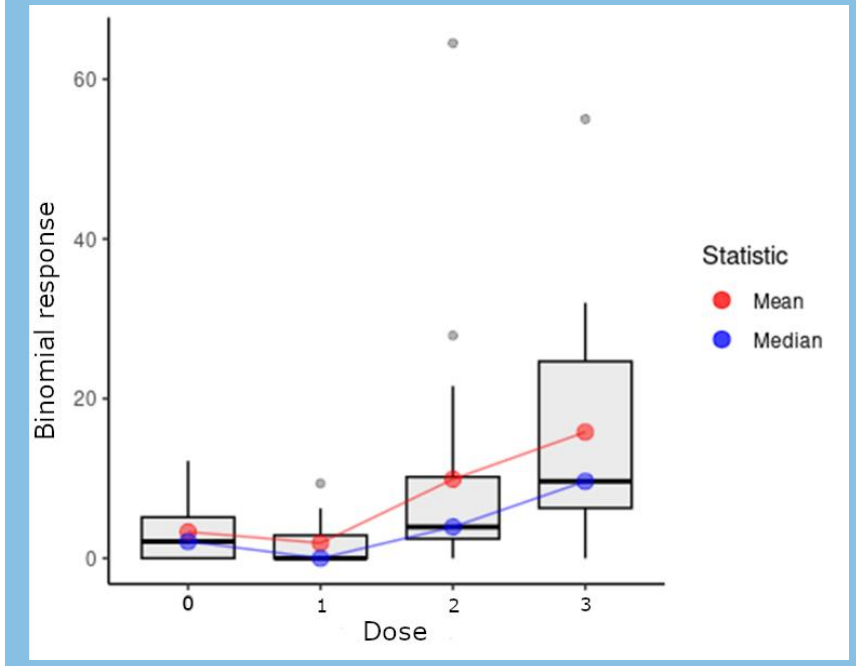
Changing Suitability for Analysis

Why does Bayes Factor Change?



Version	Bayes Factor	Message from BMABMDR
0.1.5		there is sufficient evidence that there is a substantial dose-effect
0.0.0.9082	4.85e-07	attention: there is insufficient evidence that there is a substantial dose-effect
0.0.0.9075		Version is corrupted
0.0.0.9071	1.41e-05	there is sufficient evidence that there is a substantial dose-effect
0.0.0.9060	1.52e-05	there is sufficient evidence that there is a substantial dose-effect

Changing Goodness of Fit

Why does Bayes Factor Change?

Version	GOF Bayes Factor	Message from BMABMDR
0.1.5	4.07e+73	None of the models provide an adequate fit do the data
0.0.0.9082	2.82e-86	Best fitting model fits sufficiently well
0.0.0.9075		Version is corrupted
0.0.0.9071	21.3	None of the models provide an adequate fit do the data

Changing BMDs

CLE member examples

Version	BMD10
0.0.0.9063	x
0.0.0.9065	1.9x

Version	BMD10
0.0.0.9060	36.53
0.0.0.9071	36.57
0.0.0.9082	30.67
0.1.5	36.56

CEA example (presented at SETAC)

Version	BMD10	BMD10L	BMD10U
0.0.0.9060	64772	6701	122882
0.0.0.9083	749	377	1047

Priestly S., Russell E., Crosland H., Brooks A., 2024. Benchmark Dose Modelling – Expectation vs Reality. *SETAC Seville* 2024.
https://cea.adas.co.uk/wp-content/uploads/2024/04/Priestly-et-al_BMD-modelling_SETAC-Seville-2024-1.png

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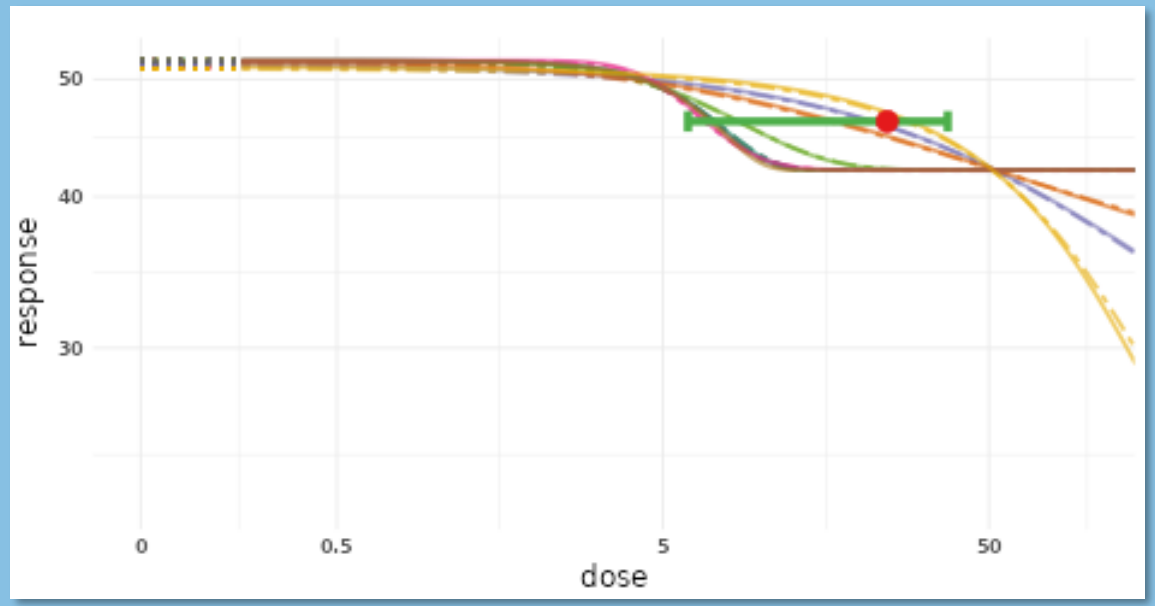
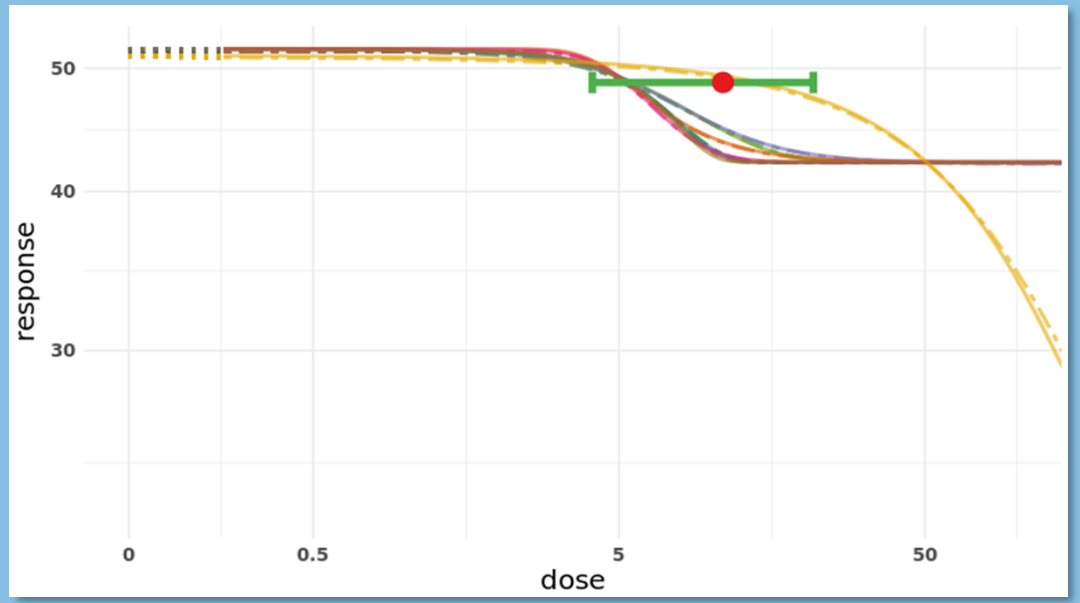
Changing the BMR

One data set is analysed to find both the BMD5 and the BMD10. The fitted models are different.



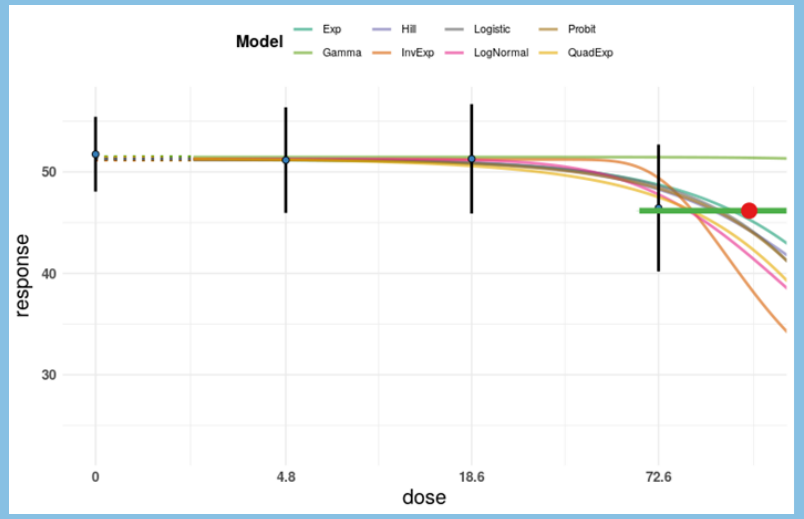


Changing the Sampling Method

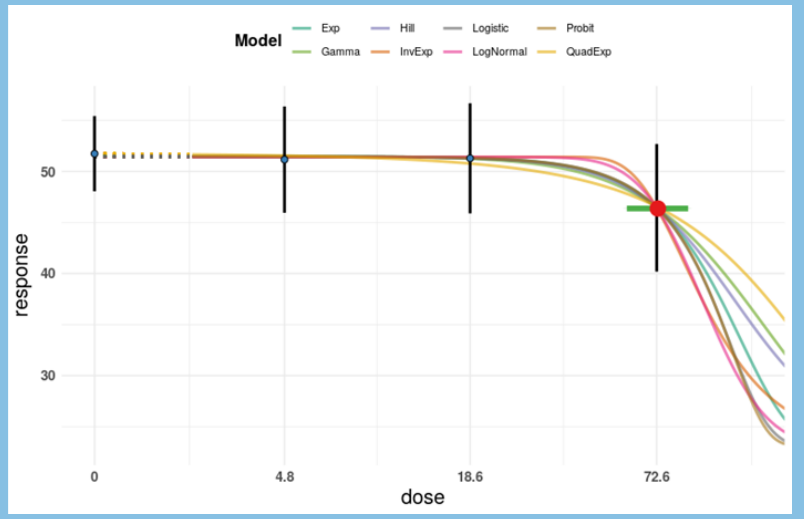
> In most cases the Laplace approximation provides reliable results, similar to the most accurate method of Bridge sampling (being more computationally demanding). Considering this, the Laplace approximation method would be the default approach given the differences in computational speed, but Bridge sampling can be requested in case of clear indications of estimation failures
>
> EFSA, 2022

We frequently find that the fitted models and therefore BMD estimates are very different for Laplace vs Bridge. Our investigation suggests that this is often due to converge issues, particularly with Bridge, and/or poor starting values.

Bridge



Laplace



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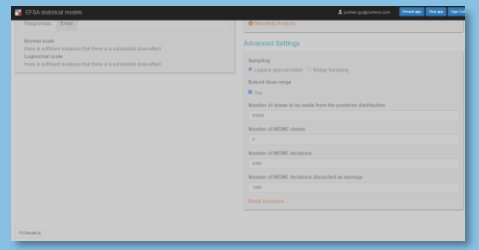
Practical Issues

R4EU Platform

Frozen platform (grey screen) without error messages.



Error messages in R code e.g.
An error was triggered when fitting model Inverse Exponential Normal for response Weight with error message: Error in quantile.default (parsIE4N$BMD * data$maxD, pvec): missing values and NaN's not allowed if 'na.rm' is FALSE

R installation

Installation requirement for R BMABMDR package is not clear. Within company environments, there have been issues with extremely long installation times and/or complete failure.

The EFSAstyle package is currently missing from the ShinyApp installation.

One BMABMDR version on zenodo (v6, 0.0.0.9075) is corrupted and cannot be installed.

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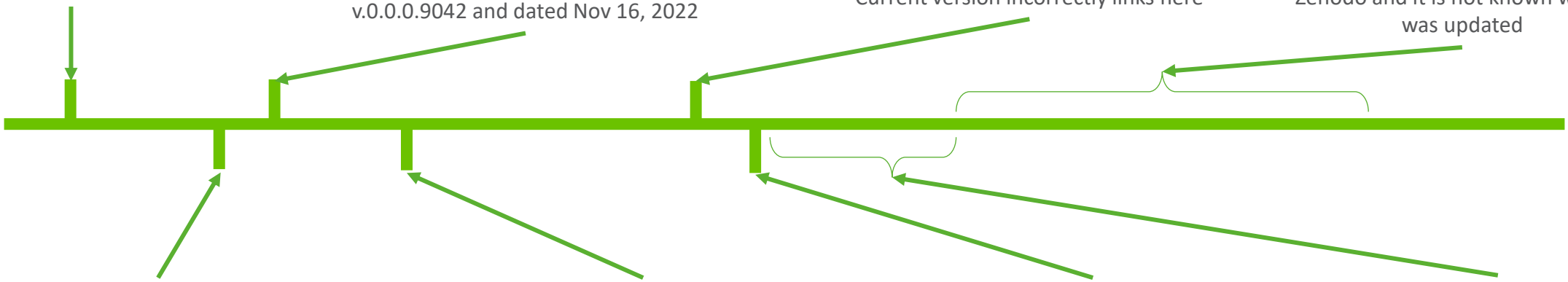
Timeline of EFSA Bayesian BMD Versions



Version 1
2022-11-16
BMABMDR: v.0.0.0.9042
https://zenodo.org/records/7334435

Version 2
2023-02-16
BMABMDR: v.0.0.0.9057
https://zenodo.org/records/7646997
Incorrectly reported as using BMABMDR v.0.0.0.9042 and dated Nov 16, 2022

Version 3
2023-03-22
BMABMDR: v.0.0.0.9057
https://zenodo.org/records/7759037
Incorrectly reported as using BMABMDR v.0.0.0.9042 and dated Nov 16, 2022

Version 4
2023-05-30
BMABMDR: v.0.0.0.9060
https://zenodo.org/records/7986184
Incorrectly dated Nov 16, 2022

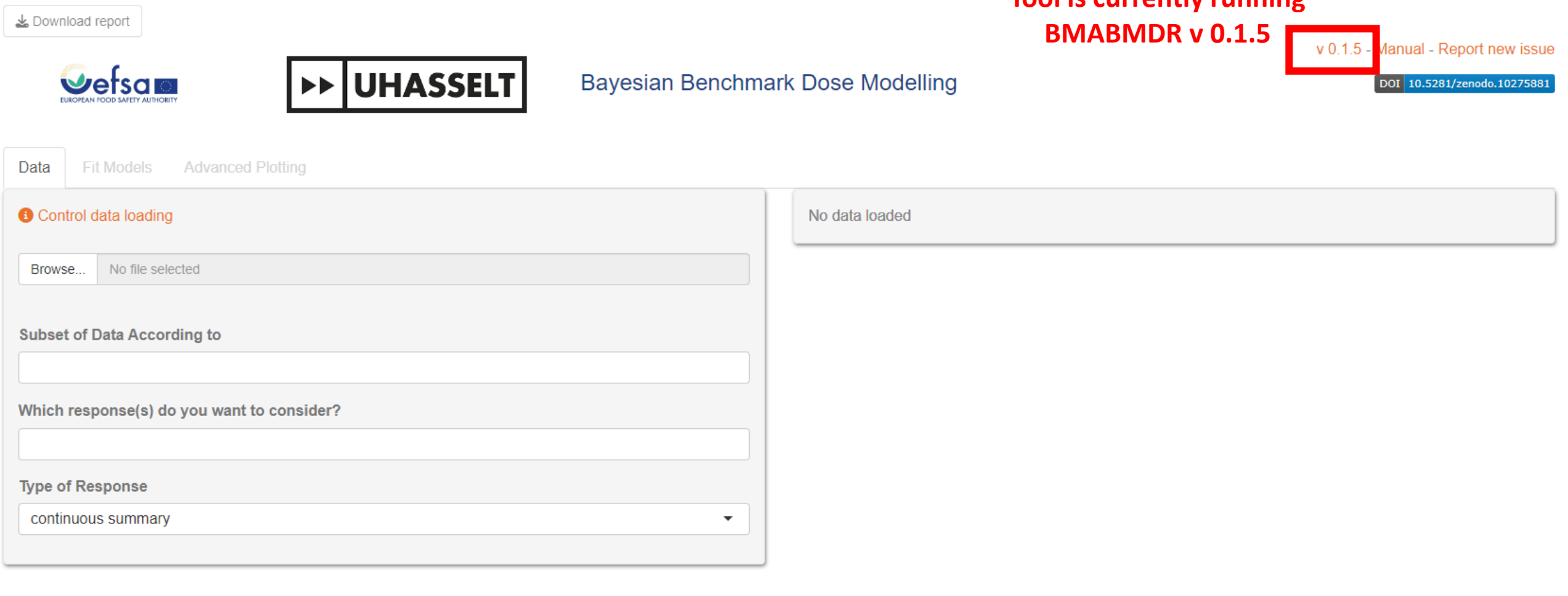
Version 5
2023-12-06
BMABMDR: v.0.0.0.9071
https://zenodo.org/records/10275881
Current version incorrectly links here

Version 6
2024-01-17
BMABMDR: v.0.0.0.9075
https://zenodo.org/records/10523648
This BMABMDR version is corrupted and cannot be installed

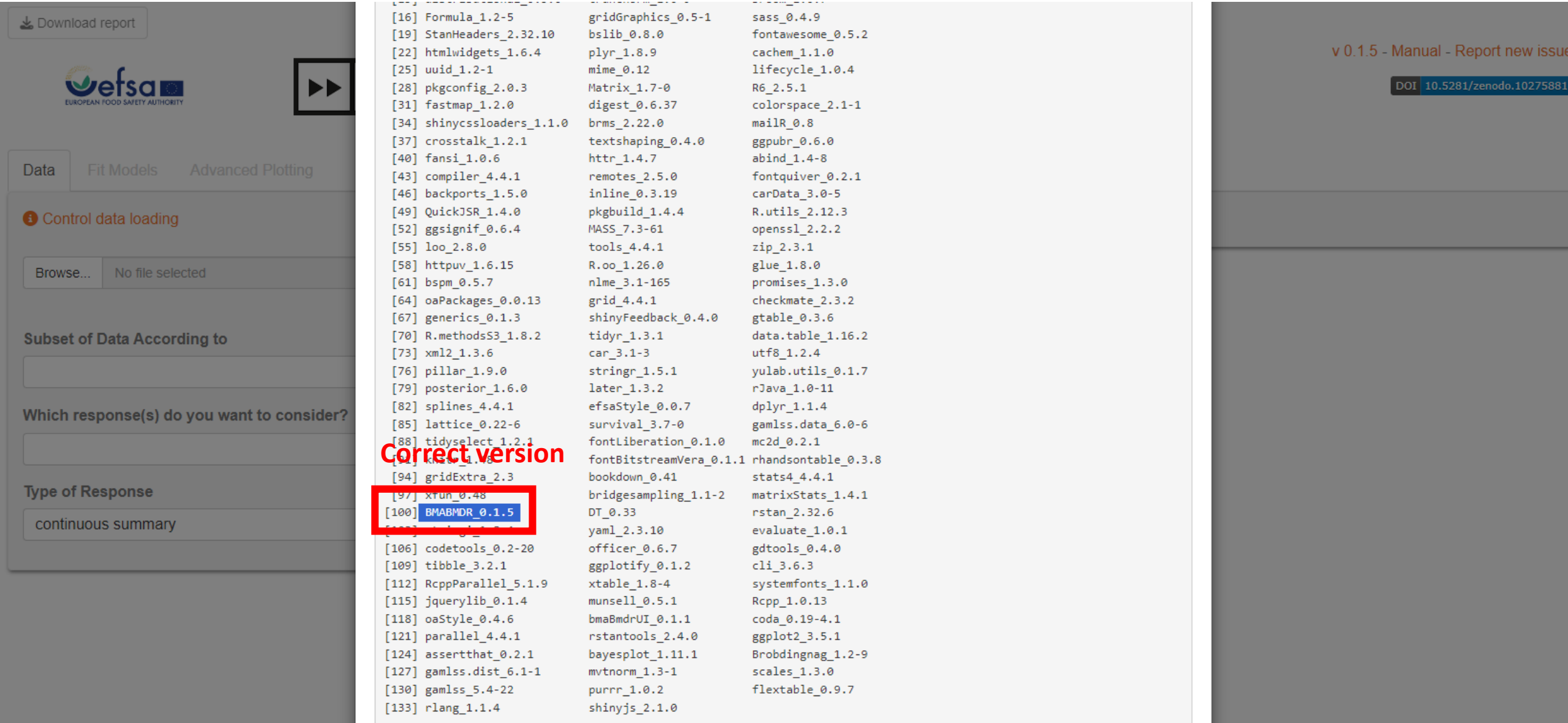
Current Version
Mid 2024
BMABMDR: v0.1.5
Current version is not archived on Zenodo and it is not known when it was updated

Intermediate version
Early 2024
BMABMDR: v.0.0.0.9082
Not available on Zenodo

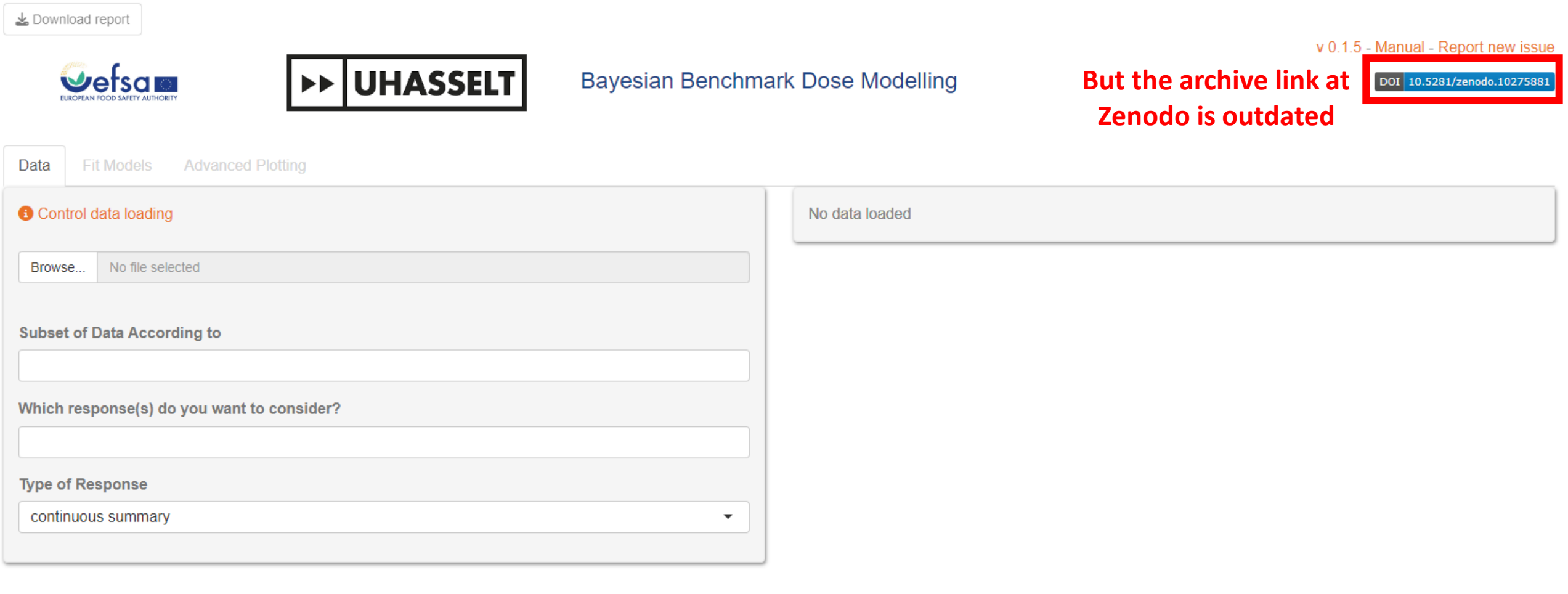
Current EFSA Bayesian BMD Tool



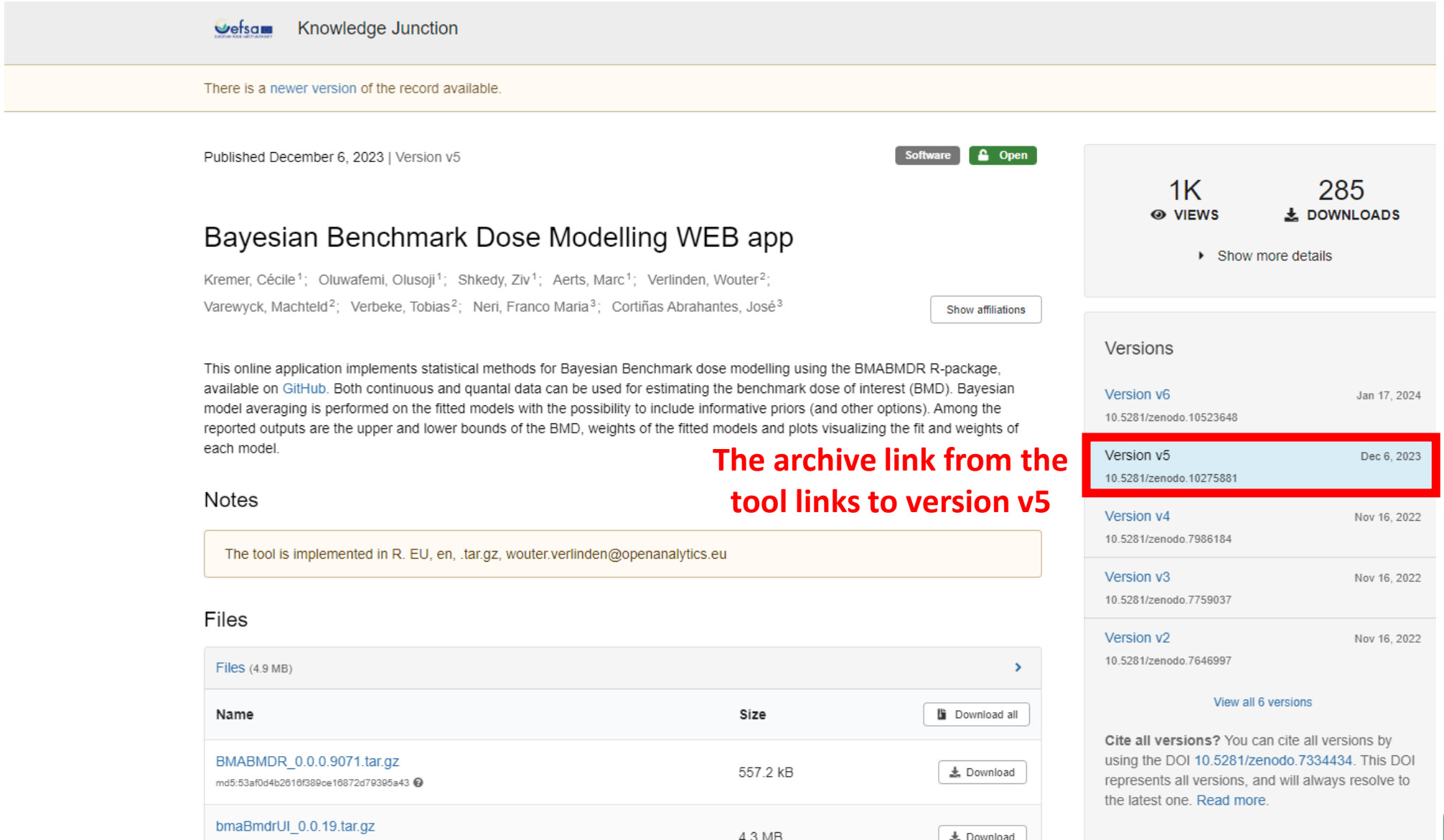
Current EFSA Bayesian BMD Tool



Current EFSA Bayesian BMD Tool



Zenodo



efsa Knowledge Junction

There is a newer version of the record available.

Published December 6, 2023 | Version v5

Software Open

Bayesian Benchmark Dose Modelling WEB app

Kremer, Cécile[1]; Oluwafemi, Olusoji[1]; Shkedy, Ziv[1]; Aerts, Marc[1]; Verlinden, Wouter[2]; Varewyck, Machteld[2]; Verbeke, Tobias[2]; Neri, Franco Maria[3]; Cortiñas Abrahantes, José[3]

Show affiliations

This online application implements statistical methods for Bayesian Benchmark dose modelling using the BMABMDR R-package, available on GitHub. Both continuous and quantal data can be used for estimating the benchmark dose of interest (BMD). Bayesian model averaging is performed on the fitted models with the possibility to include informative priors (and other options). Among the reported outputs are the upper and lower bounds of the BMD, weights of the fitted models and plots visualizing the fit and weights of each model.

Notes

The tool is implemented in R. EU, en, .tar.gz, wouter.verlinden@openanalytics.eu

Files

Files (4.9 MB)

Name	Size	Download all
BMABMDR_0.0.0.9071.tar.gz md5:53af0d4b2616f389ce16872d79395a43	557.2 kB	Download
bmaBmdrUI_0.0.19.tar.gz	4.3 MB	Download

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Versions

Version v6 10.5281/zenodo.10523648	Jan 17, 2024	
Version v5 10.5281/zenodo.10275881	Dec 6, 2023	
Version v4 10.5281/zenodo.7986184	Nov 16, 2022	
Version v3 10.5281/zenodo.7759037	Nov 16, 2022	
Version v2 10.5281/zenodo.7646997	Nov 16, 2022	

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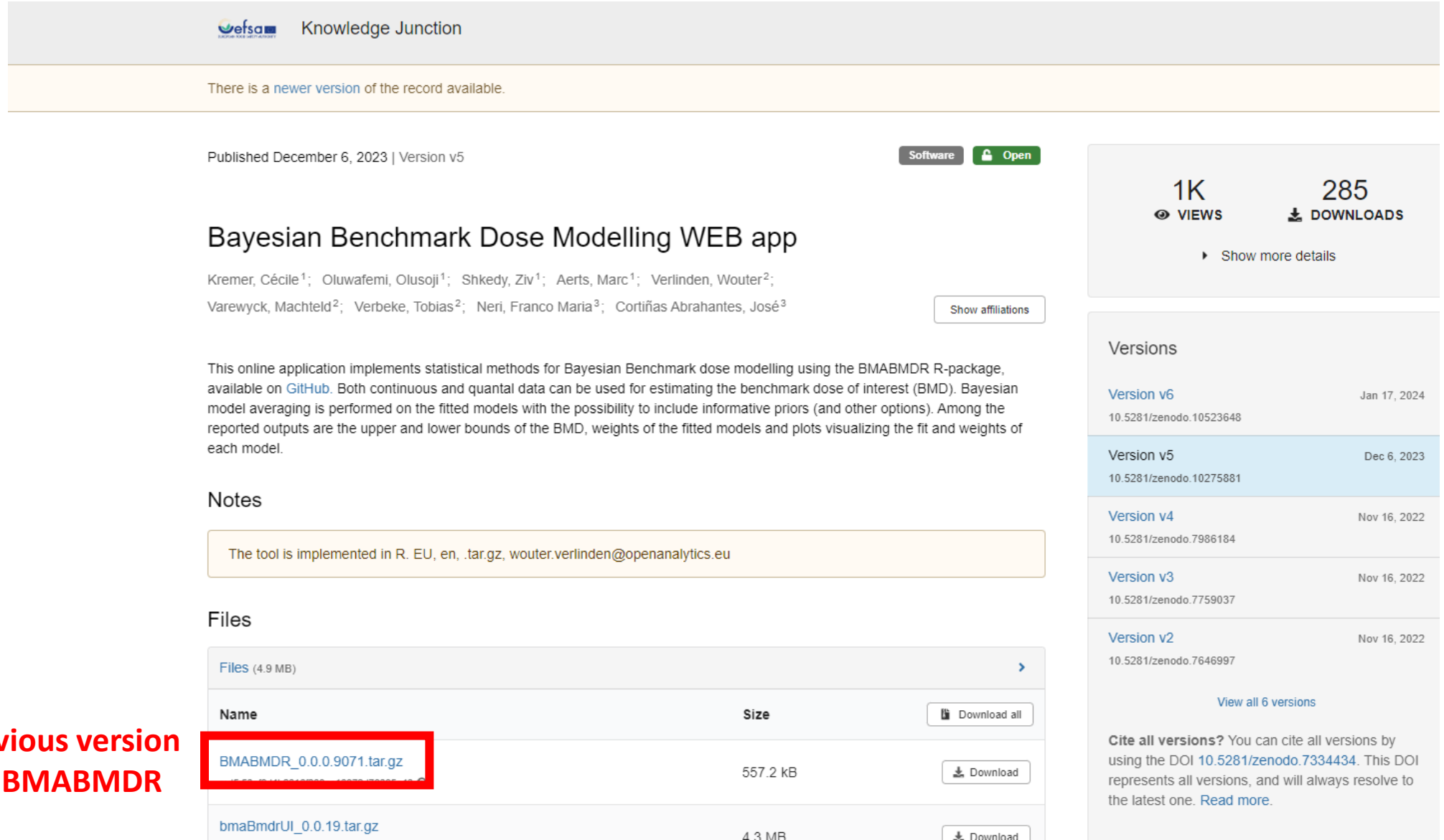
The archive link from the tool links to version v5

Zenodo



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Files

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Name	Size	Download all
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bmaBmdrUI_0.0.19.tar.gz	4.3 MB	Download

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Previous version of BMABMDR

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Files

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Name	Size	Download all
BMABMDR_0.0.0.9075.tar.gz	374.4 MB	Download
bmaBmdrUI_0.1.0.tar.gz md5:06d8cea580a1d4f728e2160d067227c2	5.1 MB	Download

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…but this is still not the BMABMDR version used by the tool

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Conclusion

The issues shown here indicate that the tool has not yet completed sufficient testing and is therefore not yet ready for regulatory use.

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Proposal for Version Control & Testing

Who are the EFSA tools developed for?

- Applicants and Member States?

- Developing software for experts vs for non-experts
  - In academia tools are often developed for other experts who have the scientific judgement to tell whether there are issues
  - Increasingly EFSA tools are used by people who may not have deep technical knowledge, and who therefore may not spot issues
  - This means the tool needs to be working as intended

Life cycle of tools and models

Scope, design, implement tool

New tool

Thorough testing:
- Bug fixes
- IT configurations
- User understanding

Regulatory vs release

- A version of the tool that can be used to set endpoint for use in risk assessments

New versions

- Update tool with scientific improvements
- Ask users what is needed to scope version updates
- New outputs, functionality, tests etc.

Version control

- A process for testing and documenting new regulatory versions before release
- Maintenance cycle (IT – e.g. compatibility Windows versions)

What testing is needed before the release of a new *regulatory* tool?

Statistical tools must be thoroughly tested:

With simulated data (so result is known)

- Check whether the tool returns correct values (validation)

With real data

- Because real data is often messy and to avoid the tool crashing or returning incorrect results

At least two sets of eyes on the code

Testing by people other than the developers is necessary

- Ideally tested by people with same level of expertise as intended users
- Testing under different computer configurations and network architectures

Documentation needed for new regulatory versions

Documentation of testing

- What and how was the testing performed?
- Which computer configuration and network architectures (domain administrators) has it been tested for e.g. local admin rights or not
- Change log (what was changed and why)

Agreed data sets for validation (simulated and real)

- Freely available so users can check it works as intended on their systems
  - e.g. as openGUTs

Types of versions

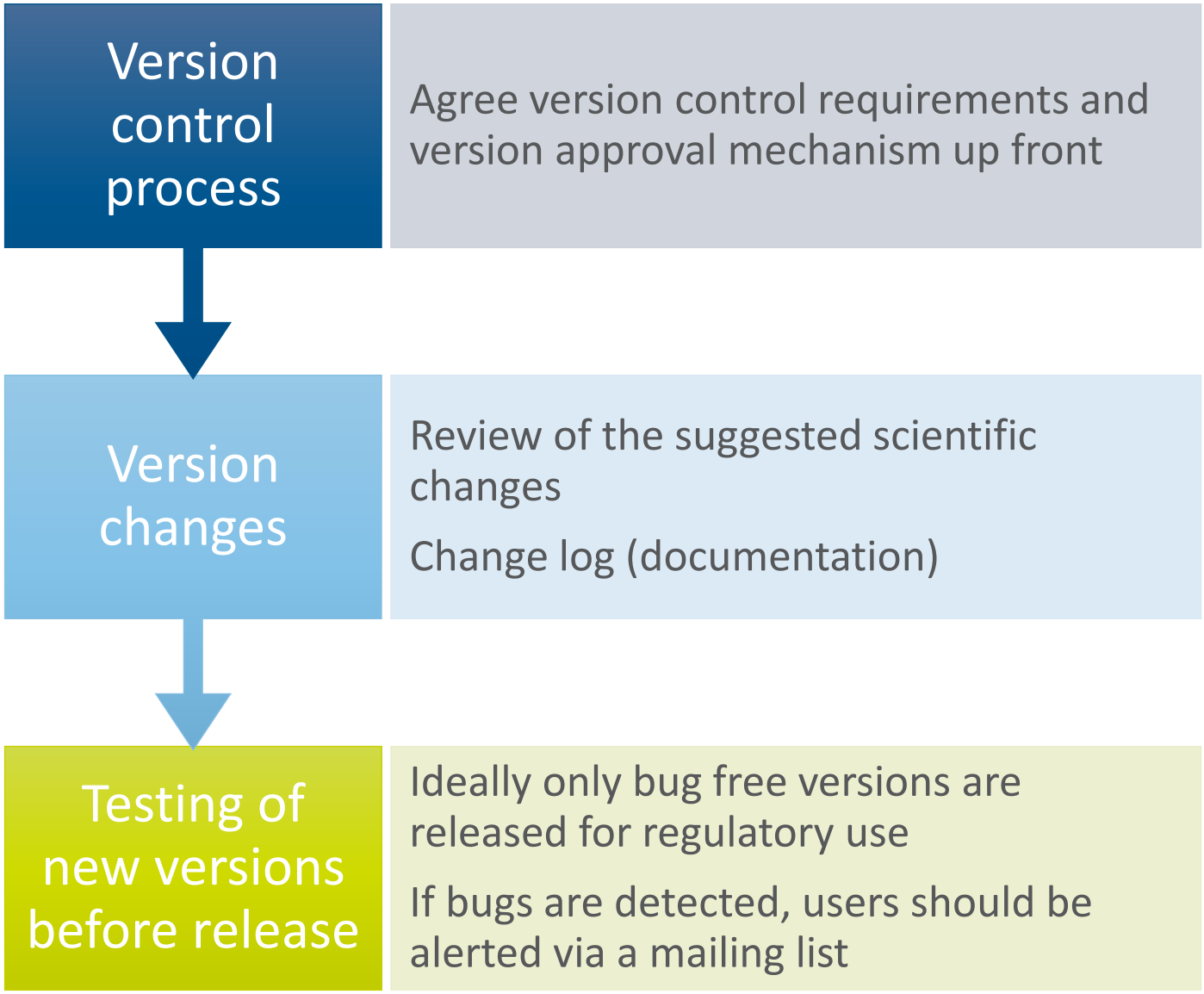
Regulatory version vs ongoing work to improving a tool

- All tools need updating over time as science advances
- Regulatory versions should not be continuously updated
  - Updates should be bundled and released e.g. once a year

The outputs from regulatory versions form the basis for decisions about registrations

- These decisions are often made several years after the dossiers were submitted
- The results from the version at time of submission should still be valid and reproducible at the time of review

Proposal for version control process



R-specific issues

Regulatory version needed

- Web version and R-package need to give same results

Code of both R package and web version needs to be archived and available for download so same version can be used at time of review

- R-code typically depend on other R-packages therefore a frozen R-environment is needed to enable running current and old regulatory versions exactly as they were when released

Outputs should be time stamped and indicate which version was used

- This enables everybody to do calculations with the version which was in force at the time of submission

Can the process for version testing and release be improved?

Could EFSA consider updating the testing requirements in contracts for outsourcing the development of tools?

Could multi-stakeholder testing groups help? This would ensure that:

- The tool is tested on different operating systems and configurations
- The tool is tested by users with different levels of expertise

BMD is open source; would EFSA consider making other tools open source too?

Industry is ready and willing to collaborate with testing

Industry's perspective on what is needed to make BMD work for wildlife risk assessment

Fully tested and validated regulatory version needed

Release of new versions: bundle changes and release e.g. once a year

- If major bugs are found, a special release is OK, but alert via mail list
- Frozen R environment (or as a minimum specify which R-package versions are needed) or use renv or similar tools
- Need a process similar to e-fate modelling version control
- Consistent process for tool release and version control for all EFSA tools, calculators and models

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Thank you for your attention!