From: Padilla Mercado, Gilberto
To: Wambaugh, John (he/him/his); Ring, Caroline (she/her/hers)
Subject: RE: trouble with fitting low bioavailability
Date: Wednesday, June 5, 2024 2:19:06 PM

Flat model best fits:
DTXSID3031862
DTXSID8031865
DTXSID4020533
DTXSID80108992

LOQs > Value:
DTXSID3061635
DTXSID4022527

Gil

From: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Sent: Wednesday, June 5, 2024 1:11 PM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Great, that works! Can you give me DTXSIDs for the chemicals that were best fit with the flat model and the ones with too high LOQ's?

Thanks!

John

From: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>
Sent: Wednesday, June 5, 2024 12:37 PM
To: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Should be fixed now! Sorry, that was a copy-paste error on my part.

Gil

From: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Sent: Wednesday, June 5, 2024 12:21 PM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Hmm, I only see 27 chemicals in that one.

John

From: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>
Sent: Wednesday, June 5, 2024 12:14 PM
To: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

No problem! I've attached the chemicals with available tkstats (we have 97 with data, 95 that are fit). The two odd ones out do have the LOQ > Concentration, which excludes them from fitting/evaluation.

Best,
Gil

From: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Sent: Wednesday, June 5, 2024 11:52 AM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

I'm so sorry. I sent the wrong file earlier. For the bakeoff I am interested in 101 chemicals in the attached file.

Thanks!

John

From: Wambaugh, John (he/him/his)
Sent: Wednesday, June 5, 2024 9:02 AM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Hi Gil – It looks like this file has only 66 chemicals in it. Do you have one that has all the chemicals from the attached file?

Thanks!

John

From: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>
Sent: Monday, June 3, 2024 3:24 PM
To: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Hi John,

I'll double check if that is the case. In the meantime, I wanted to give you the same file now updated for the

new fitting options for these select chemicals (all data transformations are applied, and bobyqa is used as the optimizer). I also suspect that it may just be that data from those four chemicals benefit from additional transformations (beyond just dose-normalized) prior to fitting.

-Gil

From: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Sent: Monday, June 3, 2024 1:47 PM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Hi Gil,

I think I am beginning to see where things went weird. In the file I have (attached) the oral bioavailability is stored as "0". Maybe a precision issue when the file was written?

John

From: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>
Sent: Monday, June 3, 2024 11:17 AM
To: Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>; Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Hello Caroline and John,

I'm back from travels and have made this comparison. To me, the starting values for Fgutabs in either calculation for these chemicals are for the most part fairly low and this is probably due to the difference in dose between oral and iv. There is around a two to three-fold difference between the proposed calculation and the current starts. Here is the comparison, where adjFgutabs is using the calculation outlined in the first email:

Chemical	Species	Reference	Media	adjFgutabs	model	param_name	start
DTXSID2020420	rat	192	plasma	0.123893	model_flat	Fgutabs	0.340523
DTXSID2020420	rat	192	plasma	0.123893	model_1comp	Fgutabs	0.499064
DTXSID2020420	rat	192	plasma	0.123893	model_2comp	Fgutabs	0.499064
DTXSID3022405	mouse	129	plasma	0.028915	model_flat	Fgutabs	0.030316
DTXSID3022405	mouse	129	plasma	0.028915	model_1comp	Fgutabs	0.002065
DTXSID3022405	mouse	129	plasma	0.028915	model_2comp	Fgutabs	0.002065
DTXSID3022405	rat	129	plasma	0.006457	model_flat	Fgutabs	0.017776
DTXSID3022405	rat	129	plasma	0.006457	model_1comp	Fgutabs	0.002166
DTXSID3022405	rat	129	plasma	0.006457	model_2comp	Fgutabs	0.002166
DTXSID7029904	rat	131	plasma	0.024588	model_flat	Fgutabs	0.13546
DTXSID7029904	rat	131	plasma	0.024588	model_1comp	Fgutabs	0.043097
DTXSID7029904	rat	131	plasma	0.024588	model_2comp	Fgutabs	0.043097
DTXSID9032329	rat	192	plasma	0.002196	model_flat	Fgutabs	0.010051

DTXSID9032329	rat	192	plasma	0.002196	model_1comp	Fgutabs	0.001516
DTXSID9032329	rat	192	plasma	0.002196	model_2comp	Fgutabs	0.001516

With the exception of propyzamide—which had Fgutabs optimized to 1.00—the rest of the chemicals seemed to have Fgutabs optimized within 10 percentage points (+/- 0.1) of either starting value.
As Caroline outlined, the change is fairly straightforward, and I can do a little testing to see if it would drastically change the final, optimized values for these chemicals and others.

Best,
Gil

From: Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Sent: Thursday, May 23, 2024 9:28 AM
To: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>; Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>
Subject: RE: trouble with fitting low bioavailability

Gil – are you still saving/outputting the start values for each parameter? If so, you could check and see how much difference there is between the current start value, and John's suggested start value, for those four chemicals. (Assuming all four of those have both oral and IV data.)

If it's very different, that's worth a try. Would involve fiddling with get_starts_1comp.R and get_starts_2comp.R. Check whether both oral and IV data exist for a chemical, and then set the starting value according to John's suggestion, rather than the current way it's set.

Then of course you'd need to re-fit the whole thing, because the new start value might change the fits for other chemicals that have both IV and oral data.

Gil – I remember at one point you changed the starting value for something else, and noted that the fits do seem to be sensitive to starting values. Is that point discussed in the manuscript? I think it's worth mentioning.

Frankly, I suspect that sensitivity to starting values might affect other PK curve fitting software, not just ours. We may not have solved that issue yet, but we can highlight it as another possible reason why different studies might report such different fitted TK parameters, and note that it becomes very obvious when you apply standardized TK fitting methods to a large CvT database.

(At one point, I saw Woody Setzer's original code for BMDS – EPA's Benchmark Dose Software for dose-response curve fitting – and he did a *lot* of work on selecting good starting values. Of course, BMDS has a whole different approach to selecting starting values, because those are totally different models with different parameters. So unfortunately we can't just borrow Woody's code, haha. But my point is that starting values do seem to matter more than I had hoped they would.)

From: Wambaugh, John (he/him/his) <Wambaugh.John@epa.gov>
Sent: Wednesday, May 22, 2024 1:07 PM
To: Padilla Mercado, Gilberto <PadillaMercado.Gilberto@epa.gov>; Ring, Caroline (she/her/hers) <Ring.Caroline@epa.gov>
Subject: trouble with fitting low bioavailability

Hi Gil and Caroline,

I'm working on the QSAR bakeoff manuscript.

I notice that the invivoPKFit fits are off for four chemicals:
2-(Perfluorooctyl)ethanol DTXSID7029904
2-Hydroxy-4-methoxybenzophenone DTXSID3022405
Bensulide DTXSID9032329
Propyzamide DTXSID2020420

In all four cases it looks like the oral bioavailability is low relative to the iv. Is it possible that the optimizer is not adjusting Fsysbio correctly? Can we set the initial value for Fsysbio to something like max(OralConc)/max(IVConc) * max(IVdose)/max(OralDose)?

John

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