

'B-compass rat' calculation tool for calculation of biomagnification factors

MANUAL

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Check www.ufz.de/b-compass-rat for updates of B-compass rat.

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1. BACKGROUND

The assessment of the bioaccumulation potential of chemicals is an important aspect in the identification of substances of potential concern for humans and the environment. In order to assess the extent of bioaccumulation in air-breathing organisms, estimation of so-called biomagnification factors (BMFs) is regarded as a meaningful approach.

It should be noted here that there are essentially three types of BMF values in the literature: The wetweight concentration ratio between an organism ($\text{mol/kg}_{\text{body}}$) and its diet ($\text{mol/kg}_{\text{diet}}$) $C_{\text{organism}}/C_{\text{diet}}$ at steady state is often referred to as BMF. However, such a concentration ratio between phases that differ in their composition is not a meaningful measure for biomagnification in a thermodynamic sense, because the concentration values do not reflect the differences in composition of organism and diet. It is thus essential to derive BMFs from measures that consider the impact of composition. This can be either done via calculating the so-called lipid-corrected (or "lipid-normalized") BMF_L or the fugacity-based BMF_F . The lipid-corrected (or "lipid-normalized") BMF_L reflects the ratio of the steady-state concentrations in body lipid ($\text{mol/kg}_{\text{lipid}}$) and diet lipid ($\text{mol/kg}_{\text{lipid}}$). This procedure makes sense for lipophilic chemicals and under the assumption that body lipid and diet lipid have similar sorption capacities for these chemicals [1]. The most mechanistic approach for calculating the BMF is the calculation using fugacities. Fugacity is a much more abstract quantity than concentration and can be best imagined as the "escaping tendency" of a molecule from its surrounding phase [2]. Differences in the fugacities between different phases are the thermodynamic cause for migration of chemicals between different phases.

In accordance with the 3Rs principle (replacement, reduction, refinement), alternatives to animal testing should be considered whenever possible. The prediction of BMFs by suitable models could be a useful approach. Important for such predictive models is that biotransformation of the chemical is represented. To consider biotransformation in the models, knowledge of the corresponding biotransformation rate constant is required. This information could be derived from *in vitro* biotransformation studies.

2. GENERAL INFORMATION ON „B-COMPASS RAT“

The B-compass rat tool presented here provides models for the calculation of BMFs using *in vitro* biotransformation data. B-compass rat allows not only hepatic biotransformation but also extrahepatic biotransformation (e.g. in the lung, gastrointestinal tract or kidneys) to be taken into account. To calculate the BMF, B-compass rat uses two models simultaneously: a simple one-compartment rat model and a more complex multi-compartment rat model. The purpose of using two models simultaneously is to ensure a worst case assessment of the bioaccumulation potential of a chemical. The multi-compartment model differs from the single-compartment model in that blood flow limitation as well as the potential first pass effect in the GIT is represented. The one-compartment model, in contrast, neglects these processes. *In vitro-in vivo*-extrapolation is performed in B-compass rat according to the recently published revised extrapolation formalism [3].

The results of both models are output simultaneously in B-compass rat. Both model calculations are based on the same minimum data input. The additional physiological information required by the multi-compartment model is already provided in the calculation tool as default values. By comparing the results of the two models, the user can evaluate if blood flow limitation and first-pass effect are relevant for calculating the BCF of the chemical of interest (i.e. if there are differences between the results of both models).

3. APPLICATION OF B-COMPASS RAT

For application of B-compass rat it is essential to activate all macros in the macro settings of Microsoft Excel (for details see [HOW TO ACTIVATE MACROS?](#)).

As described above, B-compass rat contains both a one-compartment model and a multi-compartment model for BCF calculation. The user does not have to decide which of the two models is to be used, but the results of both models are provided simultaneously without any additional effort for the user. All required rate constants, in case of the one-compartment model these are whole body rate constants, in case of the multi-compartment model organ rate constants, are calculated automatically from the input data.

To ensure clarity, B-compass rat is presented in the form of several spreadsheets. For the standard application of B-compass rat, only the "Compound input data" and "Organism input data" sheets require input from the user. The calculated BMF values can then be accessed by the user in the next sheet called "BMF".

The other spreadsheets show details of the calculation of the individual uptake and elimination processes. Here, changes by the user are only necessary if desired.

In the following, the individual spreadsheets are briefly explained:

INTRODUCTION

This spreadsheet contains a brief overview of the model structures and application of B-compass rat.

COMPOUND INPUT DATA

This spreadsheet contains a list of all substance-specific input parameters. To be entered by the user:

- Partition information
The partition information is calculated either via correlations with the octanol-water partition coefficient ($\log K_{OW}$) and octanol-air partition coefficient ($\log K_{OA}$) of the chemical.
- *in vitro*-assay information
To enter the *in vitro* information, you must first select the appropriate option from the available option fields:
 - > „S9-assay“, if *in vitro* data from S9 assays should be used
 - > „cell assay“, if *in vitro* data from cell assays should be used
 - > „microsome assay“, if *in vitro* data from microsome assays should be used
 - > „N/A“, if no *in vitro* data are available

Depending on the selected option field, input fields for assay rate constant, S9 or cell or microsome concentration, total assay volume and, in the case of cell assays, also cell viability in the assay will then be visible. From the entered data unbound fractions *in vitro* and *in vivo* as well as partition coefficients are calculated automatically.

ORGANISM INPUT DATA

This spreadsheet contains a list of all required rat physiological input parameters. The user has to enter only the bodyweight.

For the other required physiological information (blood flow rates, compositions, scaling factors) typical standard values are already provided, which do not need to be changed by the user (unless another species is to be calculated).

BMF

This spreadsheet presents the results of the BMF calculation:

- 1) „kinetic“ BMF based on fugacity basis

- a) calculated with the one-compartment model
- b) calculated with the multi-compartment model
- 2) steady-state concentration ratio and lipid-normalized BMF
 - a) calculated with the one-compartment model
 - b) calculated with the multi-compartment model
- 3) Whole-body elimination rate constant
Sum of the whole body rate constants of all elimination pathways, i.e. ventilation, biotransformation in liver, GIT, lung and kidney and excretion via feces and urine
- 4) in addition, this sheet contains two graphs illustrating the steady-state mass fluxes of the individual elimination paths relative to the mass taken up

k_1

This spreadsheet calculates the uptake rate constant k_1 via diet. In a simple approach, k_1 is calculated from feeding rate and an assumed uptake rate constant of 100 % as a worst-case estimate.

k_2 – LUNG

This spreadsheet calculates the whole body rate constant k_v for elimination via ventilation (branchial elimination) using the organism-air partition coefficient and alveolar ventilation rate. In addition, the whole-body rate constant k_v is converted to a corresponding lung elimination rate constant $k_{\text{lung,ventilation}}$, which is required in the multi-compartment model.

k_2 – HEPATIC BIOTRANSFORMATION

If the user has entered S9/cell/microsome assay *in vitro* data in the "compound input data" sheet, the hepatic *in vivo* biotransformation rate constant is calculated in the "k2 - hepatic biotransformation" sheet by *in vitro-in vivo*-extrapolation from the entered *in vitro* rate constant. Thereby, both an *in vivo* whole-body biotransformation rate $k_{B,LIVER}$ for the one-compartment model and an *in vivo* liver biotransformation rate constant $k_{\text{liver,biotransf}}$ for the multi-compartment model are calculated. In addition, this spreadsheet converts the liver blood flow rate entered in the "organism input data" sheet into rate constants that describe the transport of the chemical into and out of the liver with the blood flow.

k_2 – LUNG BIOTRANSFORMATION

This spreadsheet is analogous to the "k2 - hepatic biotransformation" sheet, except that here *in vitro* data for lung biotransformation are extrapolated.

k_2 – GIT BIOTRANSFORMATION

This spreadsheet is analogous to the "k2 - hepatic biotransformation" sheet, except that here *in vitro* data for GIT biotransformation are extrapolated.

k_2 – KIDNEY BIOTRANSFORMATION

This spreadsheet is analogous to the "k2 - hepatic biotransformation" sheet, except that here *in vitro* data for kidney biotransformation are extrapolated.

k_2 – FECES

This spreadsheet calculates the whole body rate constant k_E for the excretion of the chemical with the feces. This rate constant is calculated from feeding rate, composition of the food and assimilation efficiencies. In addition, the whole-body rate constant k_E is converted to a corresponding GIT elimination rate constant $k_{\text{GIT,feces}}$, which is required in the multi-compartment model.

k_2 – URINE

This spreadsheet calculates the whole body rate constant k_U for the excretion of the chemical with urine. This rate constant is calculated from the urination rate and the organism-water partition coefficient. In addition, the whole-body rate constant k_U is converted to a corresponding kidney elimination rate constant $k_{\text{kidney,urine}}$, which is required in the multi-compartment model.

REFERENCES

This sheet contains references for the equations and physiological parameters used.

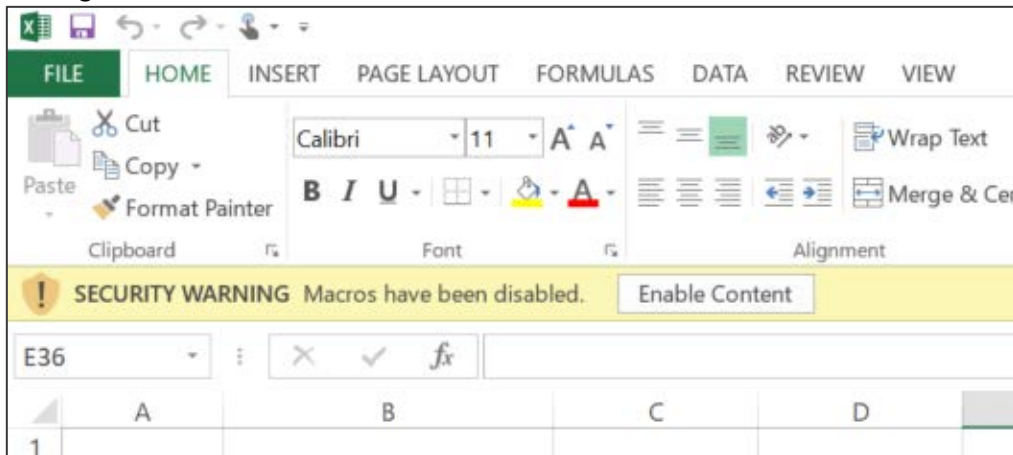
GLOSSARY

This sheet contains explanations of all variables and color codes used.

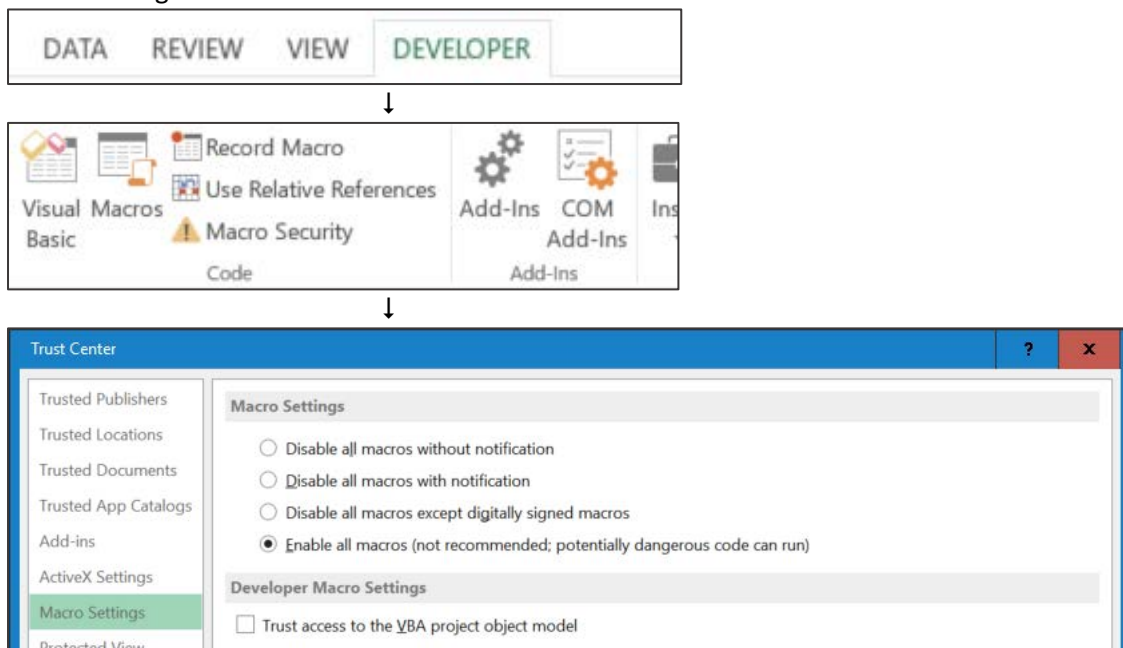
HOW TO ACTIVATE MACROS?

You can activate the macros after opening B-Compass rat

- a) by either confirming macro activation in the security warning that appears automatically by clicking on "Enable content"



- b) or by opening the „Macro Security“ dialogue box via the “Developer“ tab and setting the macro settings there to "Enable all macros".



ABBREVEATIONS AND VARIABLE NAMES

k_1	dietary uptake rate constant [g/kg/d]
k_{assay}	first-order biotransformation rate constant determined in assay [1/h]
BMF	biomagnification factor
GIT	gastrointestinal tract
k_2	elimination rate constant [L/d]
$k_{\text{B,LIVER}}$	whole-body biotransformation rate constant [1/d]
k_E	fecal egestion rate constant [1/d]
$k_{\text{lung,ventilation}}$	"lung-based" ventilation rate constant [1/d]
$k_{\text{GIT,feeces}}$	GIT fecal egestion rate constant [1/d]
$k_{\text{liver,biotransf}}$	liver biotransformation rate constant referring to liver concentration [1/d]
K_{OW}	octanol-water partition coefficient [$L_{\text{H}_2\text{O}}/L_{\text{Octanol}}$]
k_V	whole-body ventilation elimination rate constant [1/d] (also called branchial elimination rate constant)

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3. Krause, S. and K.-U. Goss, *In Vitro–in Vivo Extrapolation of Hepatic Metabolism for Different Scenarios-a Toolbox*. Chemical Research in Toxicology, 2018. **31**(11): p. 1195-1202.