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en Milieu
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User guide to the APROBA-Plus spreadsheet tool

Version 1.14

VPZ/VVH

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1 Introduction

1.1 General

The purpose of the APROBA-Plus tool is to facilitate probabilistic risk assessment of substances. It plots the uncertainty in the probabilistic health-based guidance value against the exposure uncertainty, hereby transparently visualizing the uncertainty about the distance between hazard and exposure. The underlying concepts and computational approaches are described in the "Guidance document on evaluating and expressing uncertainty in hazard characterization" (WHO-IPCS 2017), "A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects" (Chiu and Slob 2015), and in "APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances" (Bokkers et al. 2017) and are not repeated here. The APROBA-Plus tool is a Microsoft Excel workbook with four worksheets:

1. The worksheet "Hazard" performs non-probabilistic and approximate probabilistic analyses. The uncertainty in each hazard characterization aspect (PoD, Interspecies, etc.) is specified in terms of the 5% lower confidence limit (LCL = P05) and the 95% upper confidence limit (UCL = P95).
2. In the worksheet "Expo" the user can enter exposure values to obtain an ellipse plot. In this plot the uncertainty in exposure is compared with the uncertainty in the target human dose, i.e. the dose that complies with the specified protection goals.
3. The worksheet "Provisional Parameter Values" contains standard values for many of the inputs and uncertainties in the Hazard worksheet. These are either based on nominal default values or based on the generic uncertainties described and estimated in WHO-IPCS (2017).
4. The worksheet "Pick Lists" contains the allowed choices for some of the input variables in the Hazard worksheet.

The sections on the Hazard worksheet in this manual are largely based on annex 2 of WHO-IPCS (2017). All worksheets are locked, so that most cells and formulas cannot be changed. The only cells that may be changed are those for which the user may enter inputs (highlighted in light yellow).

1.2 System requirements

The APROBA-Plus tool is a Microsoft Excel file, and does not require installation, macros or administrator rights to get it working. Using APROBA-Plus requires Microsoft Excel version 2010 or higher.

1.3 Contact information

Questions, comments and suggestions to improve APROBA-Plus can be send to aproba-plus@rivm.nl

1.4 Suggested reference

To the tool:
RIVM (2023). APROBA-Plus spreadsheet tool version 1.14. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. Available at https://www.rivm.nl/en/aproba-plus

To the user guide:
RIVM (2023). User guide to the APROBA-Plus spreadsheet tool, version 1.14. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. Available at https://www.rivm.nl/en/aproba-plus

1.5 Decimal symbol

By default, Microsoft Excel uses the system separators that are defined in the regional settings of your computer. In the examples below points are used as decimal settings. If you want to change the decimal symbol of your computer, see: Change the Windows regional settings to modify the appearance of some data types - Microsoft Support

2 General layout of the Hazard worksheet

Figure 1 shows the general layout of the Hazard worksheet. As shown in this figure, there are several sections in the worksheet:

- Inputs related to the study, endpoint and protection goals (cells A1-E21);
- Inputs related to adjustment, variability and uncertainty (i.e. the aspects of hazard characterization) (cells A23-E42);
- Intermediate calculations for uncertainty analysis (cells F23-I45; A87-I131); and
- Outputs (cells A51-D61; J23-J45; A44-D48, and plot in E64).

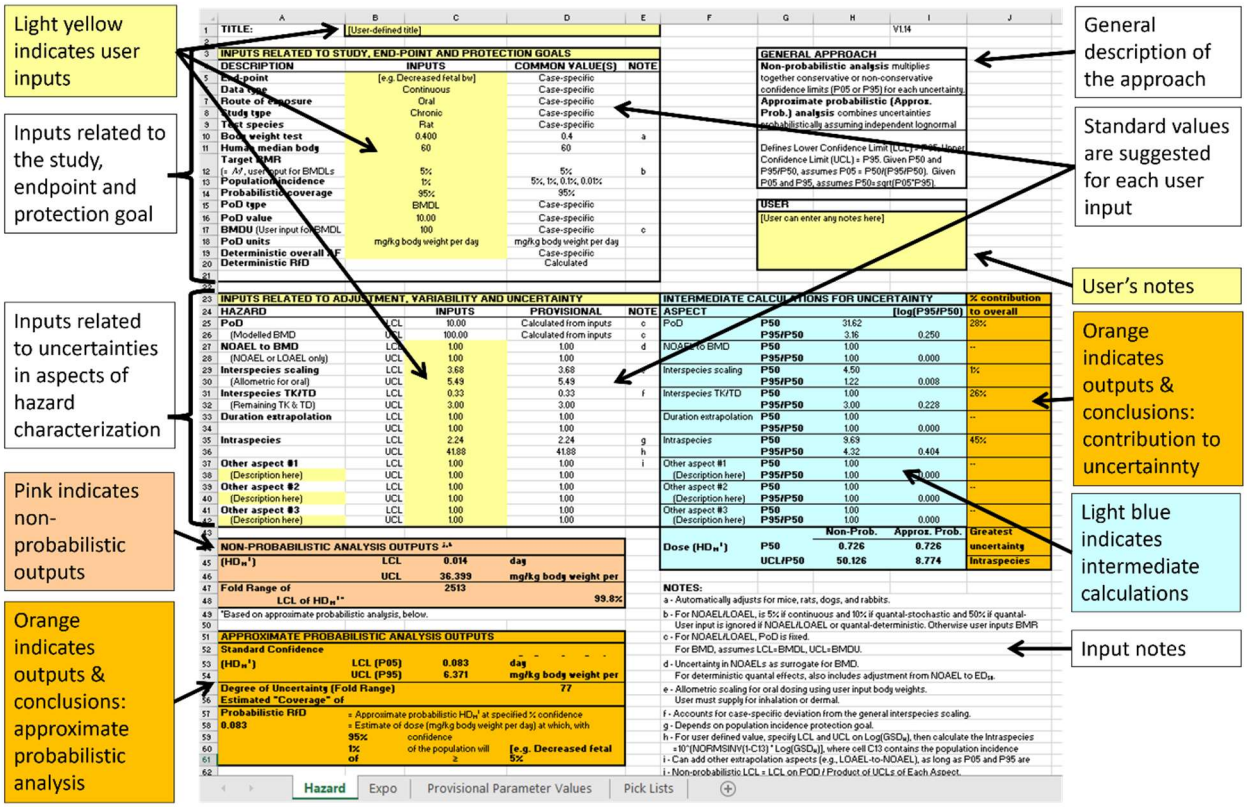

Figure 1a: General layout of the top part (rows 1 to 63) of the Hazard worksheet.

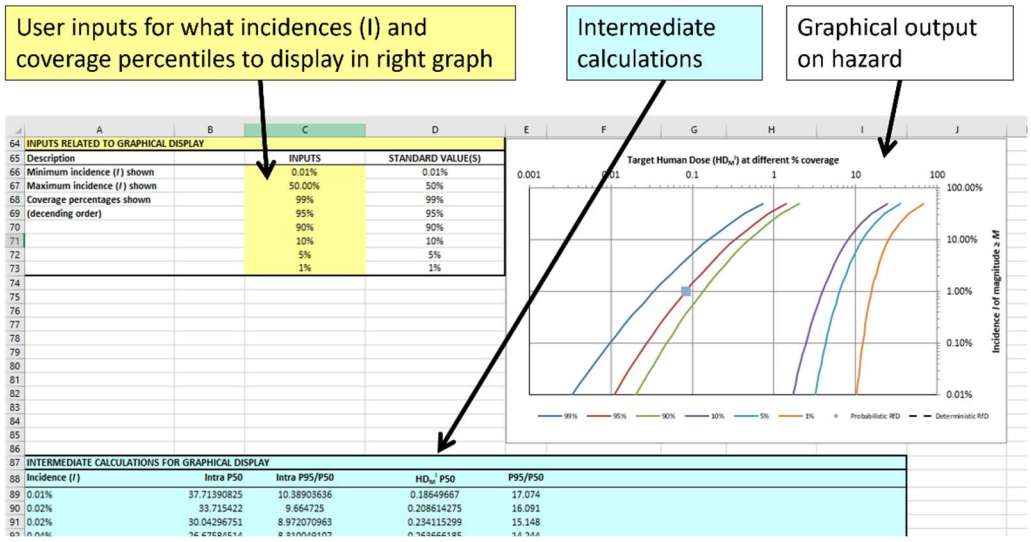

Figure 1b: General layout of the bottom part (rows 64 to 91 and further) of the Hazard worksheet.

3 General layout of the Expo(sure) worksheet

The Exposure worksheet contains three main parts (Figure 2):

1. inputs related to the exposure (row 2-12);
2. results, the plot with ellipse(s) (row 14-42);
3. intermediate calculations for graphical display of the results (row 48-135)

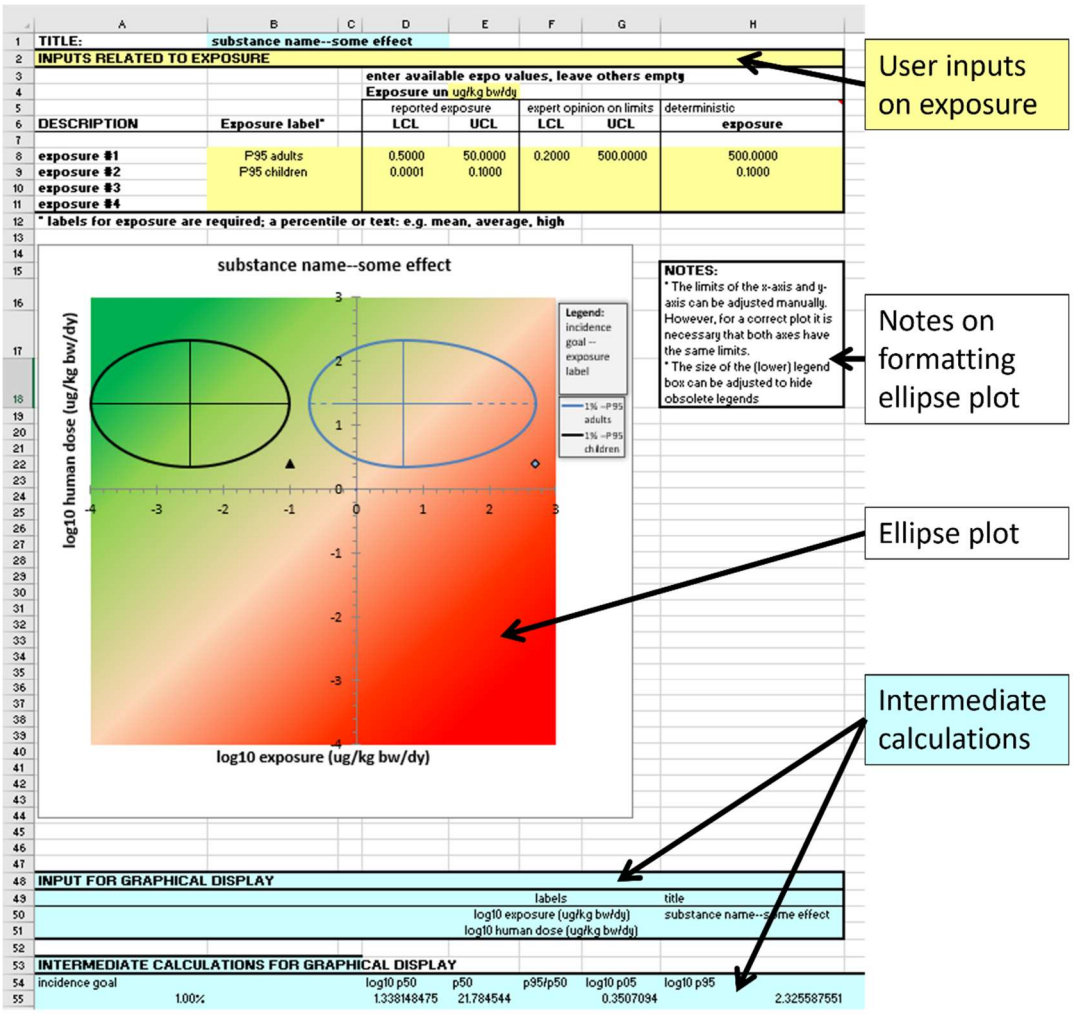

Figure 2: General layout of the Expo(sure) worksheet

4 Input APROBA-Plus

4.1 General remarks

4.1.1 Cell colour coding

Light yellow cells are inputs which can be adjusted by the user.
Light blue indicates intermediate calculations.
Pink indicates non-probabilistic outputs (confidence interval and range of uncertainty).
Orange indicates results and conclusions, i.e.:

- Approximate probabilistic outputs (standard confidence interval and range of uncertainty).
- Conclusions as to range of uncertainty, per cent coverage and a probabilistic RfD at a user-specified per cent confidence.
- Percent contribution of various aspects to overall uncertainty.

White, blue, pink, and orange cells cannot be adjusted by the user.

4.1.2 Number of decimals

For each value entered in APROBA-Plus a limited number of decimal places are available by default. If a value is entered with more decimals than available, these (exact) values are used in the calculations, but the values visible in the cells will be rounded. The number of decimal places can be adjusted manually in several ways:
One option is to click on a cell. Go to the **Number** group on the **Home** tab, and click on the  button to increase the number of decimals or on the  button to decrease the number of decimals.

4.2 Input Hazard worksheet

4.2.1 General inputs

Title (B1): Enter a title of your analysis, e.g. a chemical name. This title should not be too long because it will (together with the **endpoint**, B5) be used in the title of the ellipse plot (**Expo** worksheet). Additional notes and remarks about the analysis can be added in the **User notes** (G16)

User Notes (G16): Notes and remarks about the analysis can be added here.

4.2.2 Inputs related to the study, endpoint and protection goals (A3).

If available, standard values are suggested next to each relevant input. These may be used, or the users may enter values specific to their situation.

Endpoint (B5): Enter a description of the endpoint, e.g. "BW decrease" or "kidney lesions". The description should not be too long because it will (together with the **Title**, B1) be used in the title of the ellipse plot (**Expo** worksheet).

Data type (B6): Choose from a drop-down list with choices:

- "Continuous" for continuous endpoints.
- "Quantal-deterministic" for "deterministic" quantal end-points, where the observed dose–response relationship represents experimental variation (e.g. histological endpoints).
- "Quantal-stochastic" for "stochastic" quantal end-points, where the observed dose-response relationship represents an individual probability of developing the endpoint, such as cancer or malformations.

Data route (B7): Choose the **route of exposure** in the experimental study from a drop-down list that includes "Oral", "Inhalation" and "Dermal". Modules for other exposure routes have not been developed.

Study type (B8): Choose the study type from a drop-down list with choices "Chronic", "Subchronic", "Subacute", "Acute" or "Repro/Developmental".

Test species (B9): Choose from a drop-down list with choices "Rat", "Mouse" , "Dog", "Rabbit", "Human", or "Other".

Body weight test species (kg) (B10): Enter manually based on the body weight reported in the study. If body weights are not available from the study, common values are provided for rat, mouse, dog, rabbit and human.

Human median body weight (kg) (B11): Enter manually based on the human population whose risk is being assessed. A standard value of 60 kg is provided for reference.

Target BMR (=M, user input for BMDLs only) (B12): If BMD modelling is performed, then enter the BMR here. Standard values of 5% relative change for continuous end-points, 50% extra risk for deterministic quantal end-points and 10% extra risk for stochastic quantal end-points are provided for reference. If a NOAEL is being used as the PoD, then the standard value is automatically applied and user input is ignored.

Population incidence goal (=I) (B13): Enter the target population incidence – i.e. the fraction of the population for whom an effect of magnitude equal to the "Target BMR" would be acceptable. Standard values may be 5%, 1%, 0.1% or 0.01%.

Probabilistic coverage goal (B14): Enter the per cent confidence ("coverage") desired in the final probabilistic result. A standard value is 95%.

PoD type (B15): Choose from a drop-down list with choices "BMDL", "NOAEL" or "LOAEL".

PoD value (B16): Enter the numerical value of the PoD used in the original RfD calculation (the BMDL value, NOAEL value or LOAEL value).

BMDU (B17): If the **PoD type** is a BMD, then enter the numerical value of the BMDU derived from BMD modelling. Leave blank if the **PoD type** is NOAEL or LOAEL.

PoD units (B18): Enter the units of the PoD, such as "mg/kg bw/day".

Deterministic overall AF (B19): Enter the overall (or "composite") assessment factor (or "uncertainty factor"). This value is optional. It is used to calculate the **Deterministic RfD** (in the next row) and to plot the deterministic risk in the ellipse plot in the Expo worksheet.

4.2.3 Inputs related to adjustment, variability and uncertainty

Enter inputs related to adjustment, variability and uncertainty (i.e. the aspects of hazard characterization). If available, values are suggested next to each relevant input. These values are obtained from historical data and described (WHO-IPCS, 2017). These may be used, or users may enter values specific to their situation. For instance, if there are chemical-specific data, such as a PBK model, the standard interspecies scaling based on allometric scaling may be altered to the value appropriate for the particular compound and endpoint being characterized.
Each of the inputs is defined by its lower (LCL) and upper (UCL) confidence limit corresponding to the 5^{th} and 95^{th} percentile of the uncertainty distribution, respectively.

PoD (C25-26): This aspect addresses uncertainty in the PoD. The values are automatically calculated based on the previous user inputs.

- If the **PoD type** is BMD(L), then LCL = BMDL and UCL = BMDU.
- If the **PoD type** is NOAEL or LOAEL, the PoD is fixed and LCL = UCL = NOAEL or LOAEL.

NOAEL to BMD (C27-28): This aspect addresses the uncertainty of using a NOAEL as an estimate of the BMD (possibly after LOAEL-to-NOAEL adjustment, which can be implemented as an **Other aspect** (C37-42), see below).

- If the **PoD type** is BMDL, this aspect is not included, and both values should be set equal to 1.
- If the **PoD type** is NOAEL, standard values based on historical data are suggested, but the user can enter a different value.

Interspecies scaling (C29-30): This aspect addresses the interspecies adjustment to take into account differences in body size. Standard values for allometric scaling are suggested for the oral route of exposure, but the user can enter a different value. In case an inhalation or dermal study is considered as the critical study, no values are suggested and the user has to determine case-specific values.

Interspecies TK/TD (C31-32): This aspect addresses remaining interspecies TK and TD differences after accounting for body size differences (**interspecies scaling**). Standard values based on

historical data are suggested, but the user can enter a different value.

Duration extrapolation (C33-34): This aspect addresses uncertainty in using a less-than chronic study (as specified in "**Study type**" previously) to estimate a chronic PoD. Standard values based on historical data are suggested, but the user can enter a different value.

Intraspecies (C35-36): This aspect addresses the uncertainty in the amount of human variability in sensitivity. It depends directly on the "**population incidence goal**" entered previously. Standard values based on historical data are suggested, but the user can enter a different value. Note that if users have a different suggested LCL and UCL of the intraspecies variability $\log(GSD_H)$, they will need to calculate the LCL and UCL of $AF_{intra\text{-}I}$ associated with the specified incidence I using the formula $AF_{intra\text{-}I} = 10^{[z_{1-I} \log(GSD_H)]}$, where z_{1-I} is the z-score for normal distribution corresponding to a percentile $1 - I$.

Other aspect #1/#2/#3 (C37-42): If there are other aspects of hazard characterization that need to be incorporated, they can be added by the user in these rows. The user can specify the uncertainty for any other aspect for which no distribution has been proposed so far. When the user is able to quantify the uncertainty of any aspect in terms of two values – for example, a 5th percentile (P05) and a 95th percentile (P95) value – this translates into a lognormal distribution that can be included in the probabilistic analysis. These two values may be estimated based on any data available, in some cases based on expert judgement.

Examples of additional other aspects that need to be included in the hazard characterization are LOAEL-to-NOAEL extrapolation, high-to-low risk extrapolation, adjustment for insufficient data or an incomplete toxicology dossier and route-to-route extrapolation.

It needs to be taken into account that depending on the "other aspect" included, the description of the probabilistic RfD may no longer be correct. For example, this description depends on the PoD unit (row 18), which may be altered due to route-to-route extrapolation. The description also depends on the Target BMR (B12 or D12) which may be altered by extrapolating a relatively high incidence (10%) to a low acceptable incidence (e.g. 1/million).

4.2.4 Inputs related to graphical display

The APROBA-Plus tool includes the capability of graphically displaying the impact of different choices for coverage and incidence I on the estimate of

the HD_M^I, as well as a comparison with the deterministic and probabilistic RfDs calculated previously calculated. For interpretation of the graph see section 5.1.3. The user can provide inputs that allow for the graphical display of the impact of changing coverage and incidence I in the section "Inputs related to graphical display" (cells A64-D73).

Minimum and maximum incidence (I) shown: The user enters the lowest and highest values of population incidence I that are to be displayed in the graphic (on the y-axis).

Coverage percentages shown: The user enters different levels of coverage that are to be displayed in the graphic.

4.3 Expo(sure) worksheet

In practice, the user of APROBA-Plus will use available, existing exposure assessments, which might be a lower or a higher tier assessment for the chemical considered. When the user of APROBA-Plus is of the opinion that the available low tier exposure assessment was not sufficiently conservative or that the available higher tier exposure assessment did not include particular uncertainties, then extra uncertainty ranges can be set by expert judgement. This additional uncertainty will be plotted distinguishably from the uncertainty as reported in the available exposure assessment (see section 5.2).
This worksheet also contains the ellipse plot of the human dose and its uncertainty plotted against the exposure and its uncertainty.

4.3.1 Inputs related to exposure

Exposure unit (E4): Enter the units of the exposure, e.g. "mg/kg bw/day". The analyst should ensure that the exposure is entered in the same unit as used for the point of departure (PoD) in the Hazard worksheet, to allow for a meaningful comparison between the human dose and exposure. A warning will be given in cell F4 and in the title of the **ellipse plot** when the units do not (exactly) match.

Exposure label (B8-11): A short description should be provided on the (sub)population of which the exposure will be entered. Four different exposure estimates (e.g. related to different subpopulations or data sources) can be entered into the exposure table. Each of them requires a brief label, e.g. indicating the (sub)population and the associated percentage of the population the exposure information relates to. This label will be used in the legend of the final **ellipse plot**.

Reported exposure (D8-E11): The exposure is preferably characterized by its lower and upper confidence limit (LCL and UCL), representing the uncertainty for the exposure considered. When only a single point value exposure is available, this values can be entered as both LCL and UCL. In both situations, the assessor should ensure that the exposure confidence interval reported in the assessment document provides sufficient coverage

to be able to conclude whether the protection goals are met or not in the final outcome of APROBA-Plus. Therefore, the user needs to make a judgement on the coverage of the reported values of the exposure (interval), and, if this coverage is considered too low, expand the interval based on expert judgment to reach the required coverage (see **Expert opinion on limits**). Clearly, the coverage cannot be precisely quantified, and it needs to be assumed that it has approximate coverage, or a coverage range (EFSA 2018).

Expert opinion on limits (F8-G11): These limits are optional. The user may include additional uncertainties here. For instance, when only a single point value exposure is available, or in case uncertainties were not taken into account in the values taken from the literature, or when particular reported values are considered to be not conservative enough, i.e. the coverage is considered too low. Note that the LCL entered here should be equal or lower than the LCL entered in column D. The UCL should be equal or higher than the UCL entered in column E.

Deterministic exposure (H8-11): a deterministic value is optional. When a value is entered here, the deterministic exposure will be plotted against the deterministic RfD (from the Hazard worksheet, cell B20) in the **ellipse plot** to illustrate the level of conservatism of the deterministic risk ratios.

5 Results and (intermediate) conclusions of APROBA-Plus.

5.1 Output Hazard worksheet

5.1.1 Output on limit values

In the Hazard worksheet the following outputs and quantitative conclusions on probabilistic and non-probabilistic derivation of a limit value (e.g. RfD, ADI) will be automatically calculated:

Deterministic RfD (B20): Not user input – calculated as **PoD value** / **Deterministic overall AF**.

Non-probabilistic Target Human Dose (HD_M^I) LCL and **UCL**, and associated **fold range of uncertainty**. The only statement that can be made from those outputs alone is that the (LCL, UCL) interval has "more than 95% coverage" (cells A45-D47).

Coverage of the non-probabilistic LCL (A48-D48). This output is the per cent confidence, based on the approximate probabilistic analysis, that the actual target human dose, HD_M^I, is greater than the LCL derived from the non-probabilistic analysis.

Approximate probabilistic Target Human Dose (HD_M^I) LCL and **UCL**, and associated **fold range of uncertainty** (A53-D55). These outputs give an approximate 90% confidence interval and the associated degree of uncertainty.

Coverage of the deterministic RfD (A56-D56). This output is the per cent confidence, based on the approximate probabilistic analysis, that the actual target human dose, HD_M^I, is greater than the original RfD.

Probabilistic RfD (A57-D61). This output is the LCL of the target human dose, HD_M^I, at the user-specified per cent confidence, based on the approximate probabilistic analysis. It is described as the "Estimate of the dose [units] at which, with [user-specified per cent] confidence, [user-specified population incidence goal per cent] of the population will have [user-entered end-point] of magnitude greater than [user-specified target BMR].

5.1.2 Output on contribution to uncertainty

The "intermediate calculations" shown in the Hazard worksheet may give useful results in terms of deciding whether to conduct additional analysis, modelling or data generation. The column marked "% contribution to overall uncertainty" (J23-J45) gives the percentage of the overall uncertainty in HD_M^I that is contributed by each hazard characterization aspect. This information can help prioritize efforts to reduce uncertainty. For instance, if NOAEL to BMDL uncertainty is among the greatest sources of uncertainty, then deriving a BMD confidence interval could significantly reduce uncertainty. If the data set is not amenable to such analysis, then additional experiments designed so that BMD modelling is feasible could be a priority. Alternatively, if duration extrapolation is among the greatest sources of uncertainty, then additional longer-duration studies may significantly reduce uncertainty. Overall, however, the "% contribution to overall uncertainty" provide valuable insight from the probabilistic calculations into the relative contributions of different sources of uncertainty.

5.1.3 Graphical output on the impact of changing coverage and incidence I

The APROBA-Plus tool also includes the capability of graphically displaying the impact of different choices for coverage and incidence I on the estimate of the HD_M^I, as well as a comparison with the deterministic and probabilistic RfDs calculated previously calculated. The user can provide inputs that allow for the graphical display of the impact of changing coverage and incidence I in the section "Inputs related to graphical display" (cells A64-D73), with a screenshot of graph where this capability is controlled shown in Figure 3. The format of the graphic (axes, colours, line styles, etc.) itself can be modified per standard features in Microsoft Excel.

In Figure 3 it can be seen that the probabilistic RfD of 0.08 (x-axis) protects 99% of the population (y-axis, 1-I=1%) with 95% confidence (prob RfD lies on the red line corresponding to 95% coverage). The graph indicates that if 99.9% of the population should be protected (with 95% confidence), then the probabilistic RfD should be approximately 0.03 (follow the red 95% coverage curve down to 0.10% incidence (y-axis) and deduct corresponding value on x-axis.
In this graph, the coordinates of a point on one of the plotted lines or curves can be obtained by hoovering the mouse pointer over the point of interest.
When 99% confidence is demanded (at I=1%), then the probabilistic RfD shifts horizontally to the left, to the 99% coverage percentage, also at a human dose of approx. 0.03 dose units (x-axis).
Obviously, the above calculations can also be made by adjusting the incidence goal (I, cell B13) and coverage goal (cell B14) respectively.
The dashed line indicates the deterministic RfD, here 0.2 dose units (x-axis), and shows that the coverage of the deterministic RfD is less than 90% (at I=1%), because the dashed line intersects the 1% incidence (y-axis) below (right) the green 90% coverage curve. Another conclusion that could be drawn is that (with 95% confidence) the incidence at the deterministic RfD is ~5% (intersection of dashed and red 95% coverage curve).

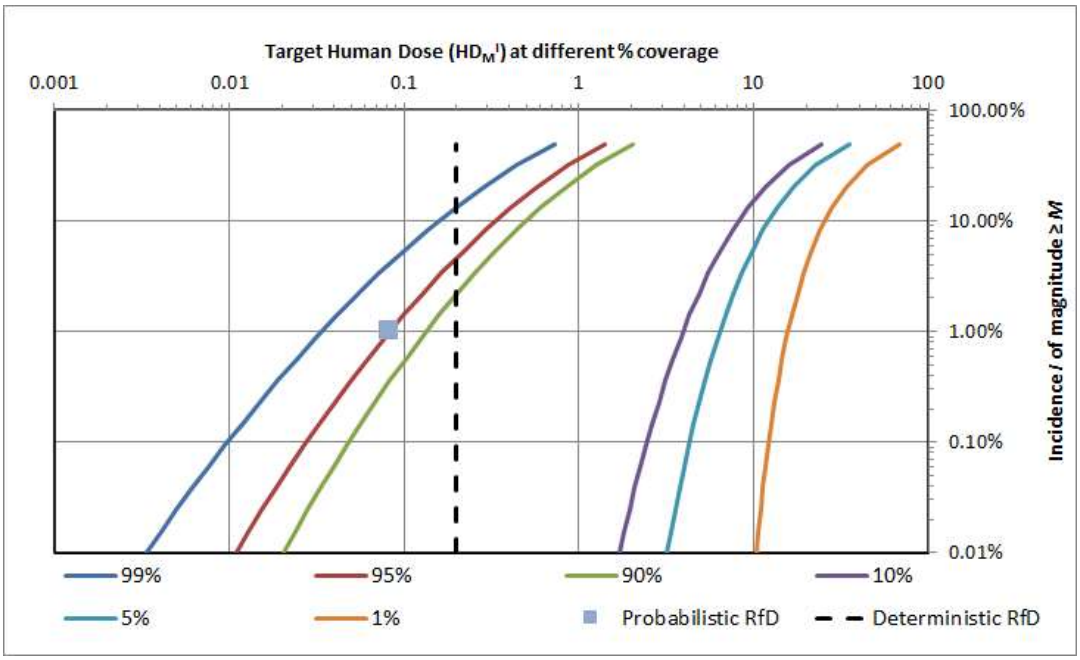

Figure3: Example of graphical output on the impact of changing coverage and incidence I. See text for explanation of the graph.

5.2 Output Expo worksheet, the ellipse plot

5.2.1 General remarks

Once the inputs for evaluating the hazard and the exposure uncertainties have been entered in APROBA-Plus the uncertainty range for the HD_M^I is graphically compared with the uncertainty range for the exposure. Figure

4 shows an example of the ellipse plot, with the exposure uncertainty on the x-axis and the HD_M^I uncertainty on the y-axis. The HD_M^I is depicted as a solid (vertical) line representing its confidence interval. The confidence interval of the exposure percentile is presented as a solid (horizontal) line representing data-based uncertainties, while the dashed extension indicates the additional uncertainties that were based on expert judgment (if applicable). The two lines intersect at the midpoint of the HD_M^I range and the midpoint of the (reported) exposure range (both on log-scale). The vertical line indicating the human exposure is plotted at the midpoint of the (reported) LCL and UCL rather than the additional (dashed) LCL and UCL. The overall uncertainty is represented by the ellipse that is drawn around the plotted confidence interval cross. This ellipse indicates where the combination of the true HD_M^I and true exposure characteristic might be, given the information available.

It is not useful to divide the uncertainty distribution for the exposure percentile by the uncertainty distribution of the HD_M^I, analogous to the calculation of a risk ratio. The subpopulations in the numerator and denominator do not relate to the same groups of individuals, and the resulting ratio would only allow for a conservative estimate. However, the differences between both subpopulations may be overlooked and the main sources of uncertainty cannot be identified anymore, because a single metric is reported. Taking a ratio of hazard and exposure values is only meaningful if this is done on the level of the individual (as in e.g. IPRA, van der Voet and Slob, 2007) as it does not make sense to compare the critical dose of one individual with the exposure in another.

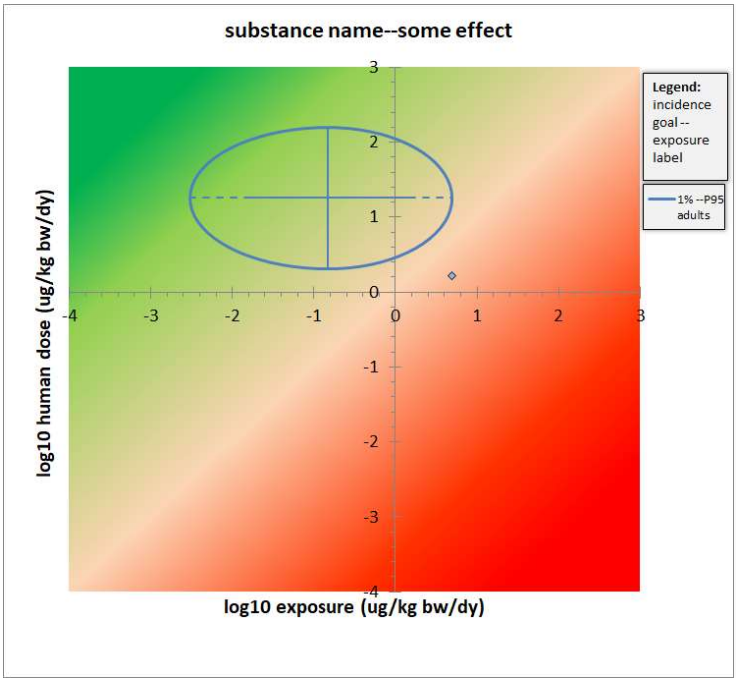

Figure 4: Example of the ellipse plot. See text for explanation of the plot

5.2.2 Shape of the ellipse

The above considerations are part of the reasons that APROBA-Plus shows both the uncertainty in the target human dose and the uncertainty in exposure separately, and compares them in a plot, rather than reduce them to a single dimension by division. Yet another reason is that in this way it is directly visible how much larger the uncertainty in one direction is compared to the other direction (Figure 5). If refinement of the risk assessment is needed, the graph provides visual guidance on what type of information (hazard, exposure, or both) is likely to provide the greatest improvement (Embry et al., 2014), as illustrated below. When it is considered more effective to reduce the uncertainty in the target human dose, the Hazard sheet includes further information on the relative contributions from the various aspects to the overall uncertainty in the HD_M^I (section 5.1.2).

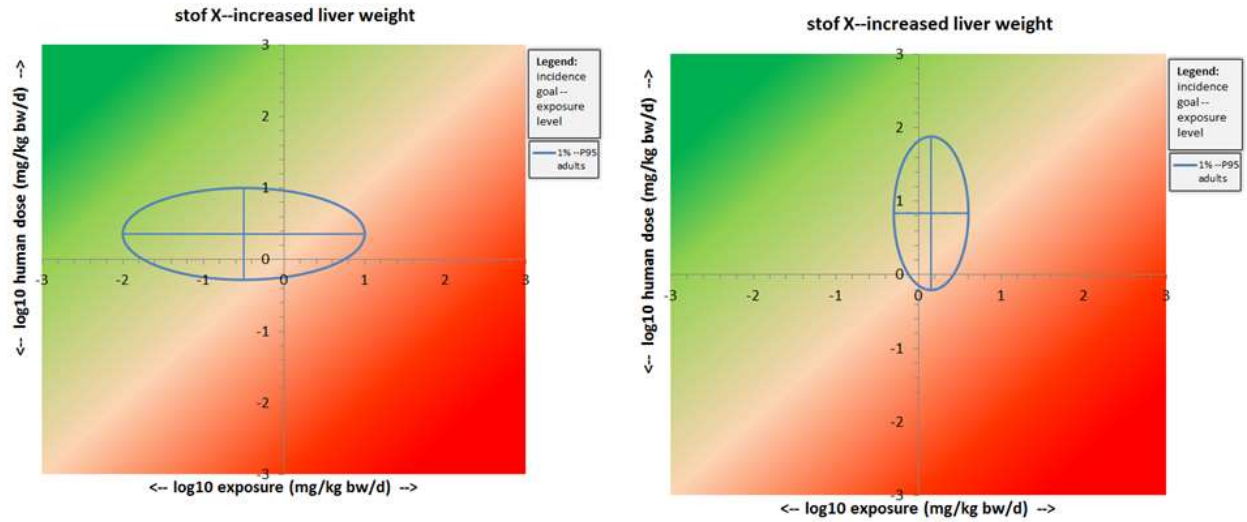

Figure 5: illustrations of analyses where the uncertainty in the exposure is larger compared to the uncertainty in the hazard (left), or the other way around (right)

5.2.3 Location of the ellipse

APROBA-Plus does not draw the line where exposure equals the HD_M^I as that would suggest a level of precision that is not realistic. Instead, the distance to the identity line is indicated by different shades of green (exposure < HD_M^I) and red (exposure > HD_M^I).

- When the whole ellipse is clearly located in the green area of the plot, then the (true) exposure most likely is below the (true) HD_M^I, and the protection goals are most likely to be met (where "most likely" means close to the assumed coverage).
- When the ellipse is completely located in the red area, this indicates that the exposure most likely exceeds the HD_M^I, and the protection goals (in terms of M and I) would not be met.
- In case the ellipse is located in both the green and the red area a conclusive answer cannot be given, and various options may be

considered. When most of the ellipse lies in the green area, the odds are that the exposure is smaller than the HD_M^I, but this cannot be stated with the assumed confidence level (as a small fraction of the ellipse lies in the red area). In that case a full probabilistic risk assessment (IPRA) might be considered. Another option to consider is to obtain additional data to reduce the uncertainty either in the exposure or in the HD_M^I. Here, it may be taken into account which specific uncertainties contribute most to the overall uncertainty; this information is shown by the APROBA-Plus output (cells J23-J45).

5.2.4 Deterministic RfD vs. exposure

When a value for the deterministic RfD is obtained (cell B20 of the Hazard worksheet) and deterministic exposure(s) is entered in the Expo worksheet (cells H8-11), the deterministic exposure will be plotted against the deterministic RfD (e.g. diamond symbols in Figure 4) to illustrate the conservatism of the deterministic risk ratio(s).

5.2.5 User options to adjust the ellipse plot

The **title** of the ellipse plot is a combination of the descriptions provided by the user in cells B1 and B5 of the Hazard worksheet. By changing the information in these two cells, the title of the ellipse plot can be adjusted.
A warning will be given in when the units of the human dose (y-axis) and exposure (x-axis) do not exactly match.

The limits (or bounds) of the **x-axis** and **y-axis** can be adjusted manually: right click the axis and select "Format axis", then in "Axis Options" adjust "Bounds". **Note** that for a correct plot it is necessary that both axis have the same bounds.

The **legend** consists of two boxes. The upper box denotes what description is given in the lower box, namely the incidence goal defined in the Hazard sheet (B13) and the Exposure label (B8-B11). The size of the lower legend box can be adjusted to hide obsolete legends.

The user can to change all graph settings at their own risk, using the standard features in Microsoft Excel.

6 References

Bokkers BGH, Mengelers MJ, Bakker MI, Chiu WA & Slob W. (2017) APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances. Food Chem Toxicol, 110, 408-417. https://doi.org/10.1016/j.fct.2017.10.038

Chiu WA and Slob W (2015). A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. Environmental Health Perspectives 123, 1241-54.

EFSA (2018) Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 2018;16(1):5123 https://doi.org/10.2903/j.efsa.2018.5123

Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M, Dewhurst IC, Doerrer NG, Hines RN, Moretto A, Pastoor TP, Phillips RD, Rowlands JC, Tanir JY, Wolf DC & Doe JE (2014) Risk assessment in the 21st
century: roadmap and matrix. Crit. Rev. Toxicol. 44 (Suppl. 3), 6–16.

van der Voet H & Slob W (2007) Integration of probabilistic exposure assessment and
probabilistic hazard characterization. Risk Anal. 27, 351–371
https://doi.org/10.1111/j.1539-6924.2007.00887.x

WHO-IPCS (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization– 2nd edition. IPCS harmonization project document ; no. 11. ISBN 978-92-4-151354-8. Geneva: World Health Organization.
https://www.who.int/publications/i/item/9789241513548