BfR
German Federal Institute for Risk Assessment

Using APROBA for integrated TDI derivation and uncertainty analysis - the case of BPA

Workshop: Advancing Quantitative Analysis in Human Health Assessments through Probabilistic Methods
07.10.2024, US EPA RTP

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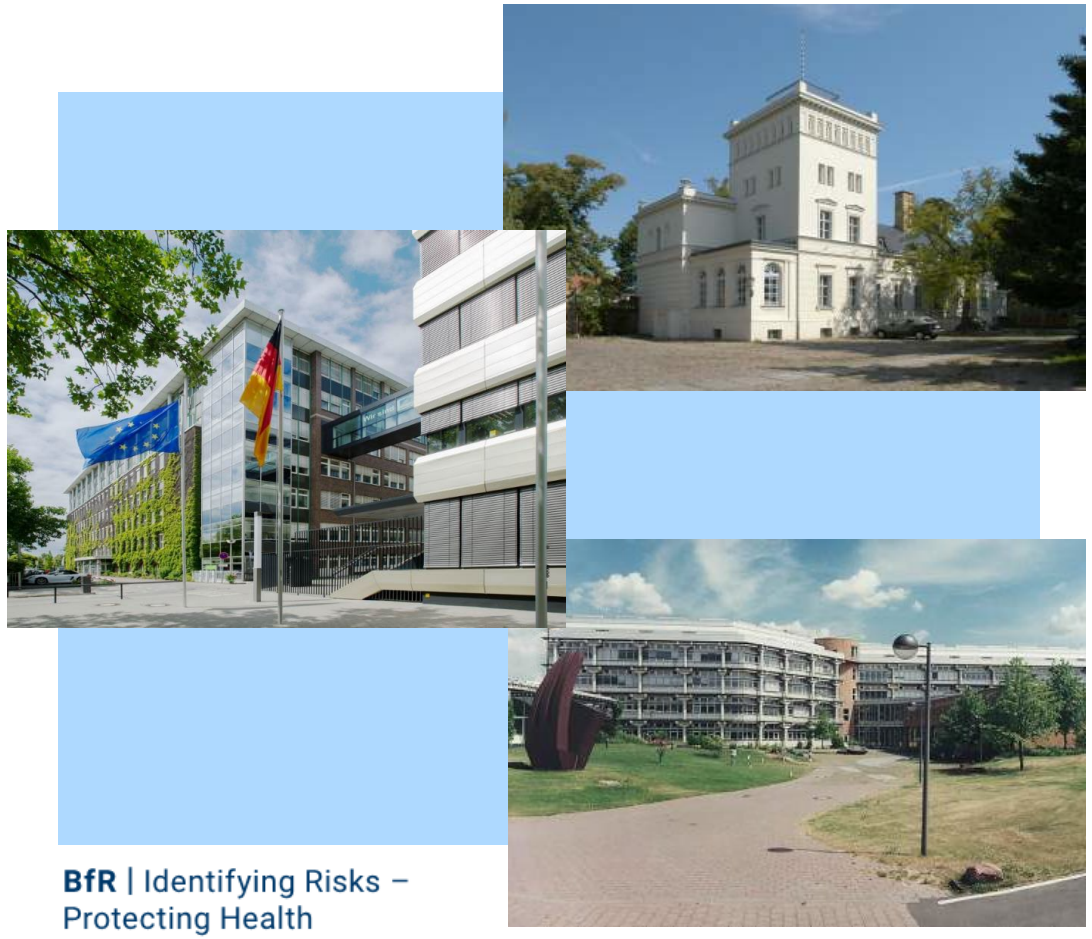
https://bfr.bund.de/en



- Part of the portfolio of the **Federal Ministry of Food and Agriculture** (BMEL)
- Founded in 2002, three locations in **Berlin, Germany,** 9 Depts, 21 National Reference Labs
- Remit (inter alia): scientific **opinions and assessments related to food and consumer safety**, counsel to policy level, research related to statutory tasks
- **2023**: ca. 1180 employees (> 500 scientists), annual budget 134 M€ + 9 M€ 3rd party funding, 2622 scientific opinions, 283 publications, 993 presentations

Disclaimers

The views expressed in this presentation **may or may not represent** those of others, including the BfR.

This presentation is **not about the correct TDI for BPA**, only about how we derived one using an (approximate) probabilistic method.

Background – recent work on Bisphenol A (BPA)

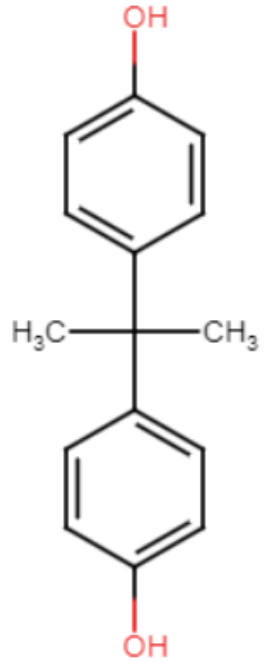
TDI: Estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health. (EFSA)

12/21: EFSA draft opinion on BPA, **TDI = 0.04 ng/kg bw/d**

→ 1/100.000 of previous, temporary TDI, < 1/60 of TTC for genotoxic carcinogens!
https://open.efsa.europa.eu/consultations/a0c1v00000JA9rGAAT

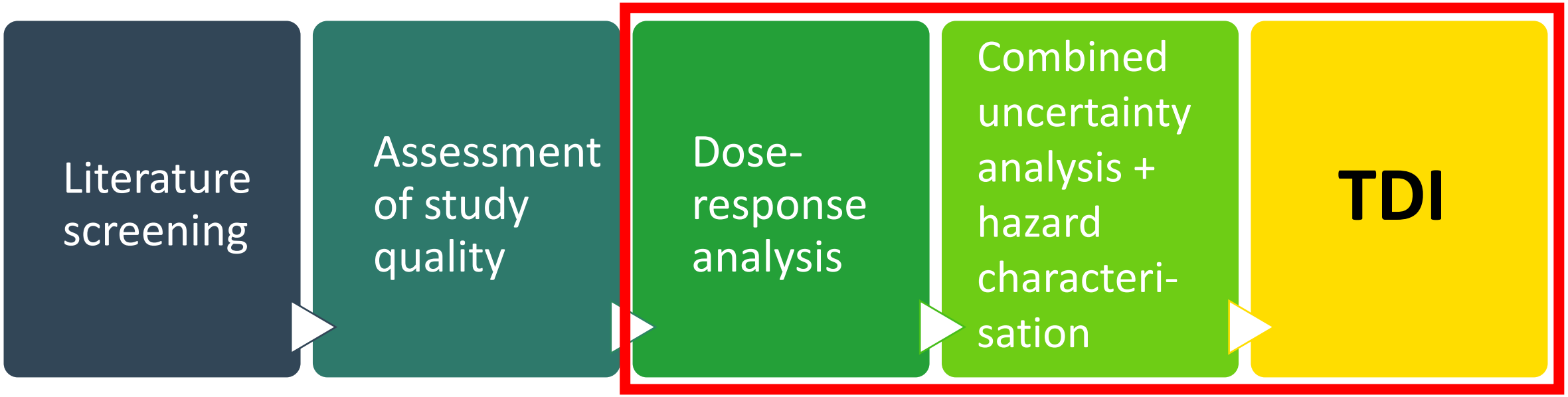
Public consultation: BfR, EMA **divergence** with EFSA
https://www.efsa.europa.eu/sites/default/files/2023-04/bfr-efsa-art-30.pdf,
https://www.efsa.europa.eu/sites/default/files/2023-04/ema-efsa-article-30.pdf

04/23: EFSA raises TDI to **0.2 ng/kg bw/d**, BfR publishes TDI of **0.2 µg/kg bw/d**
https://doi.org/10.2903/j.efsa.2023.6857, https://doi.org/10.17590/20230419-14234-0



Bisphenol A

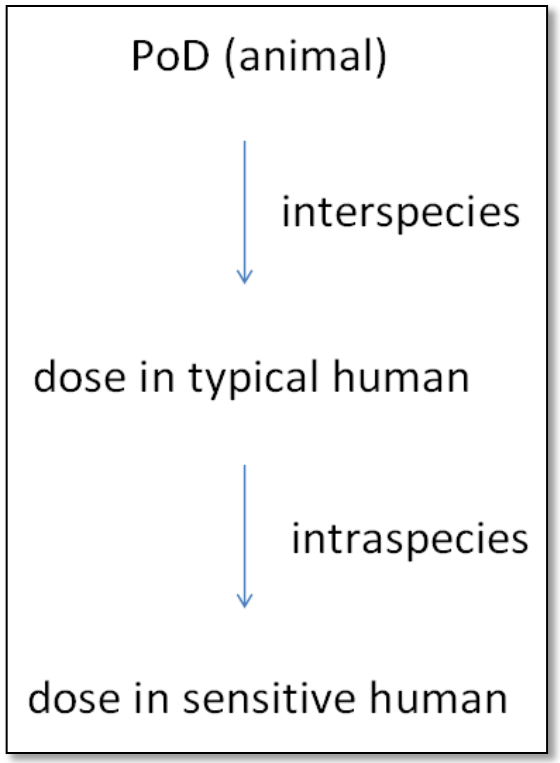
Methodology used to develop BfR opinion



This presentation

Deterministic approach to hazard characterisation (HC)

Derivation of a Reference Dose (RfD) / Health-Based Guidance Value (HBGV)



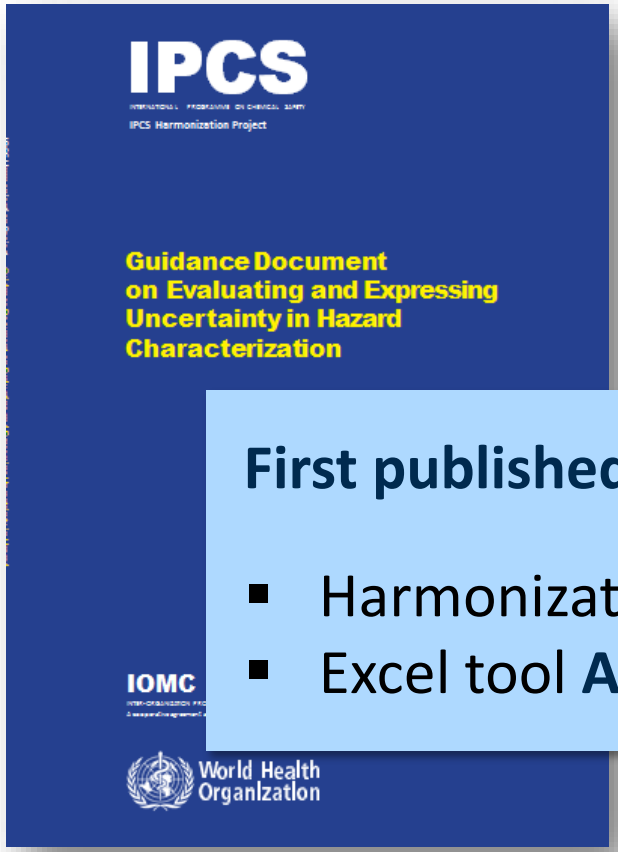
Toxicological **Point of Departure (PoD**, e.g. NOAEL/LOAEL, BMDL) is divided by **Assessment Factors (AF)**:

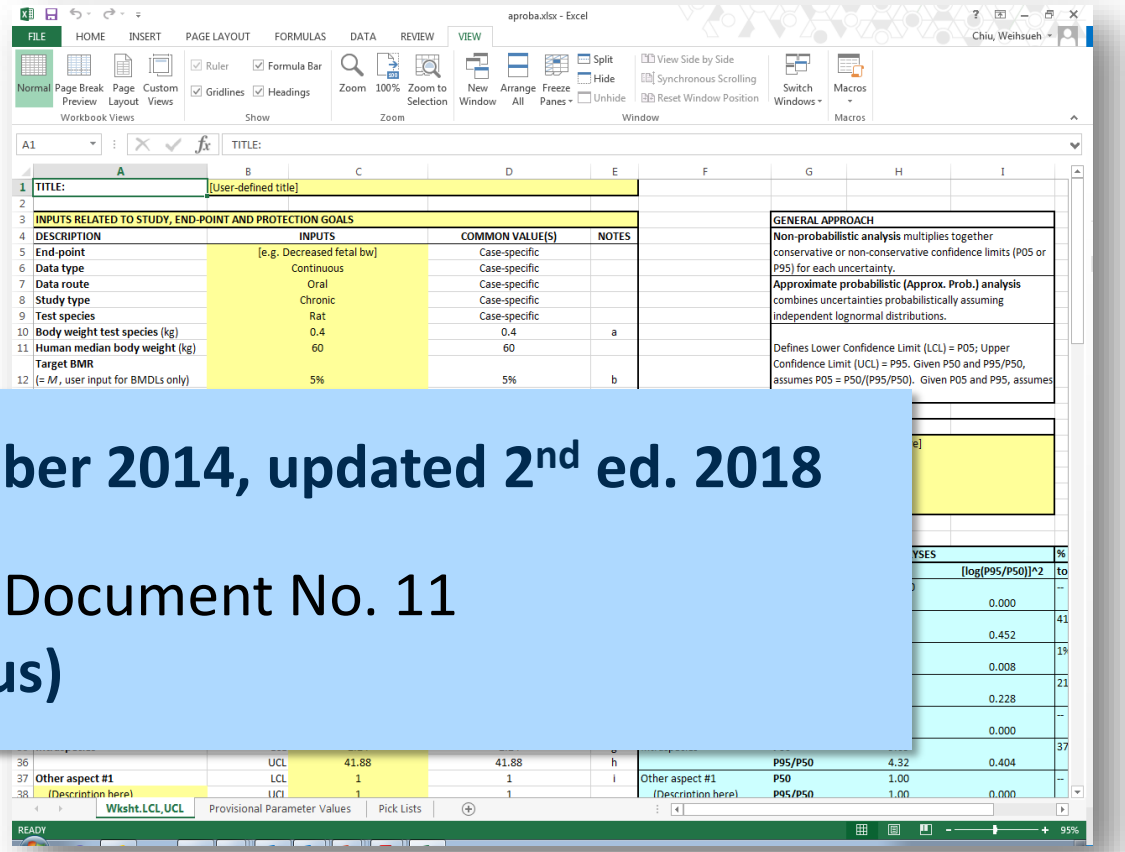
$$RfD = \frac{PoD}{AF_1 \times AF_2 \times AF_3 \times \cdots}$$

- Over all chemicals and scenarios, AFs **conceptually** represent something between „covers most cases“ and „worst case“.
- However, for a given extrapolation from animals to humans, multiplying worst cases may result in extreme conservatism: **If AF cover 95 %** of cases, combination covers **99.75 %** (2 AF), **99.9875 %** (3 AF), **99.999375 %** (4 AF)

Conservatism of risk assessments **needs to be balanced** to avoid unwanted consequences.
Problem: conservatism in **AFs** is **not precisely known**.

Approximate probabilistic assessment - APROBA





First published in September 2014, updated 2nd ed. 2018

- Harmonization Project Document No. 11
- Excel tool **APROBA(-Plus)**

https://apps.who.int/iris/handle/10665/259858

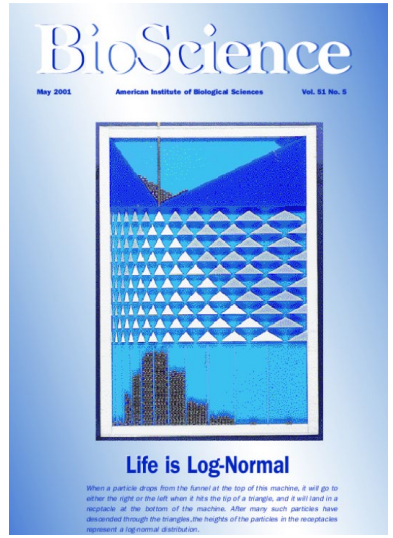
https://www.rivm.nl/en/aproba-plus

Approximate probabilistic assessment - APROBA

Uncertainty in each HC aspect is **not considered by using** (more or less) **conservative point estimates** (AFs or a lower-bound PoD), but by an **LCL-UCL range** or **probability distribution** instead.

Why "**approximate**"?

- Instead of applying full-scale Monte Carlo analysis, probability distributions are **approximated as lognormal.**
- **P50 (median) and P95 sufficient** to construct distribution, can be **estimated** if unknown, even via informed guess.



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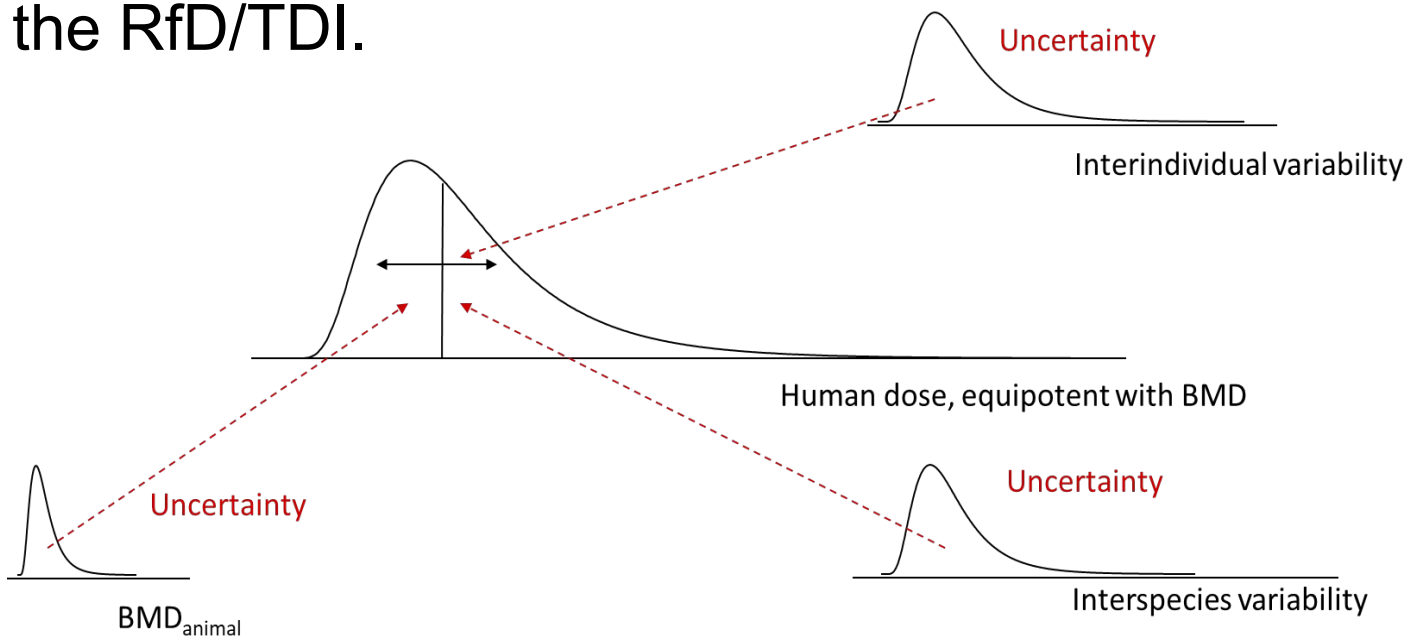
Approximate probabilistic assessment - APROBA

Individual HC aspect distributions are then combined into an **overall uncertainty distribution** for the RfD/TDI.



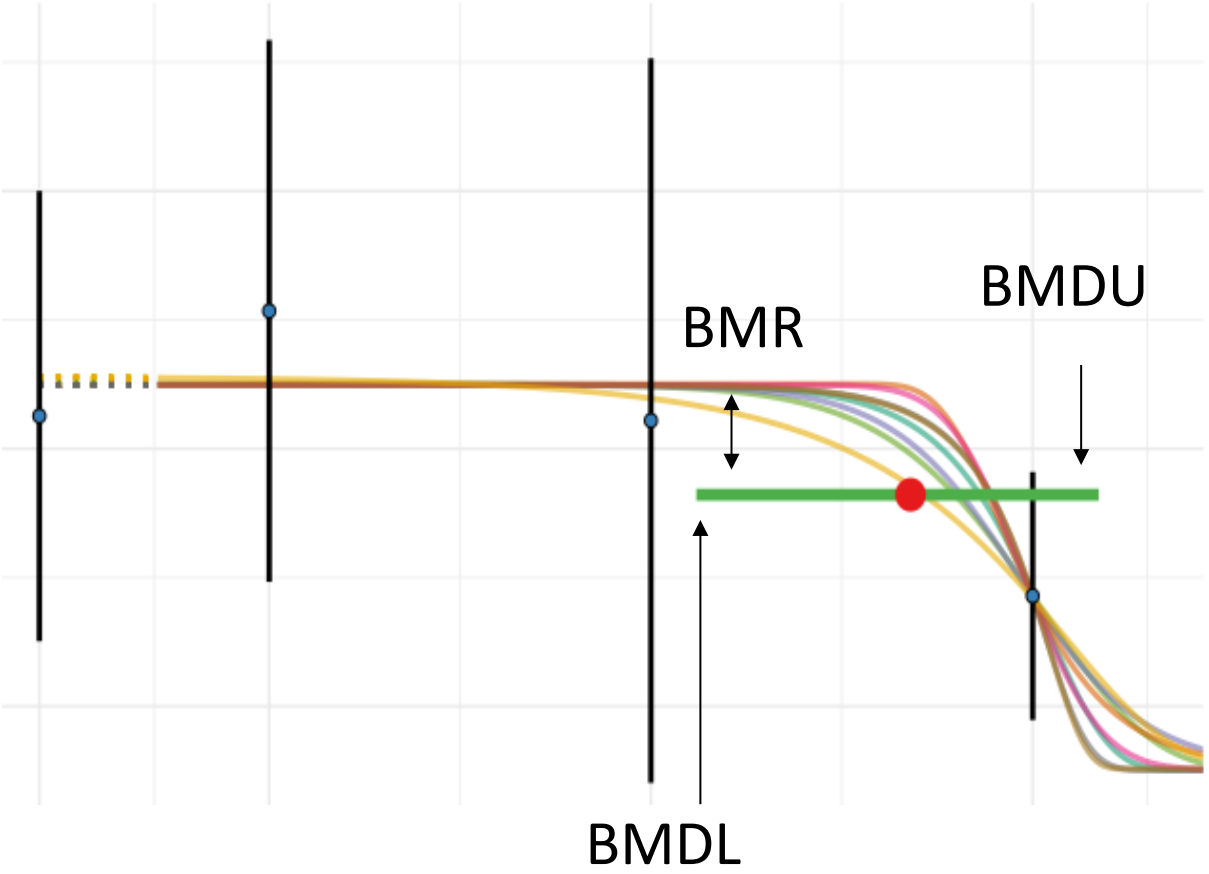
TDI derivation and uncertainty analysis are not separated. Rather, the TDI is determined from dose-response and uncertainty analysis **in an integrated way**.

Dose-response analysis

All Tier 1 + Tier 2 studies

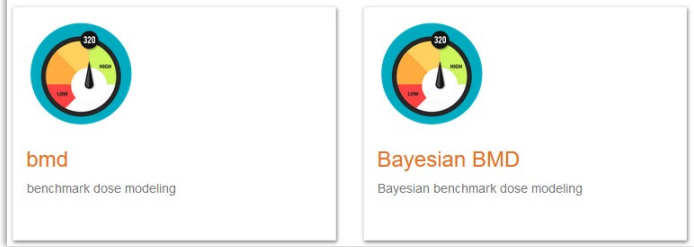
Benchmark Dose Modelling
acc. to EFSA guidance (2022)
https://doi.org/10.2903/j.efsa.2022.7584

Effect size (BMR) 10 %
(except immunotox)



Dose-response analysis

https://r4eu.efsa.europa.eu



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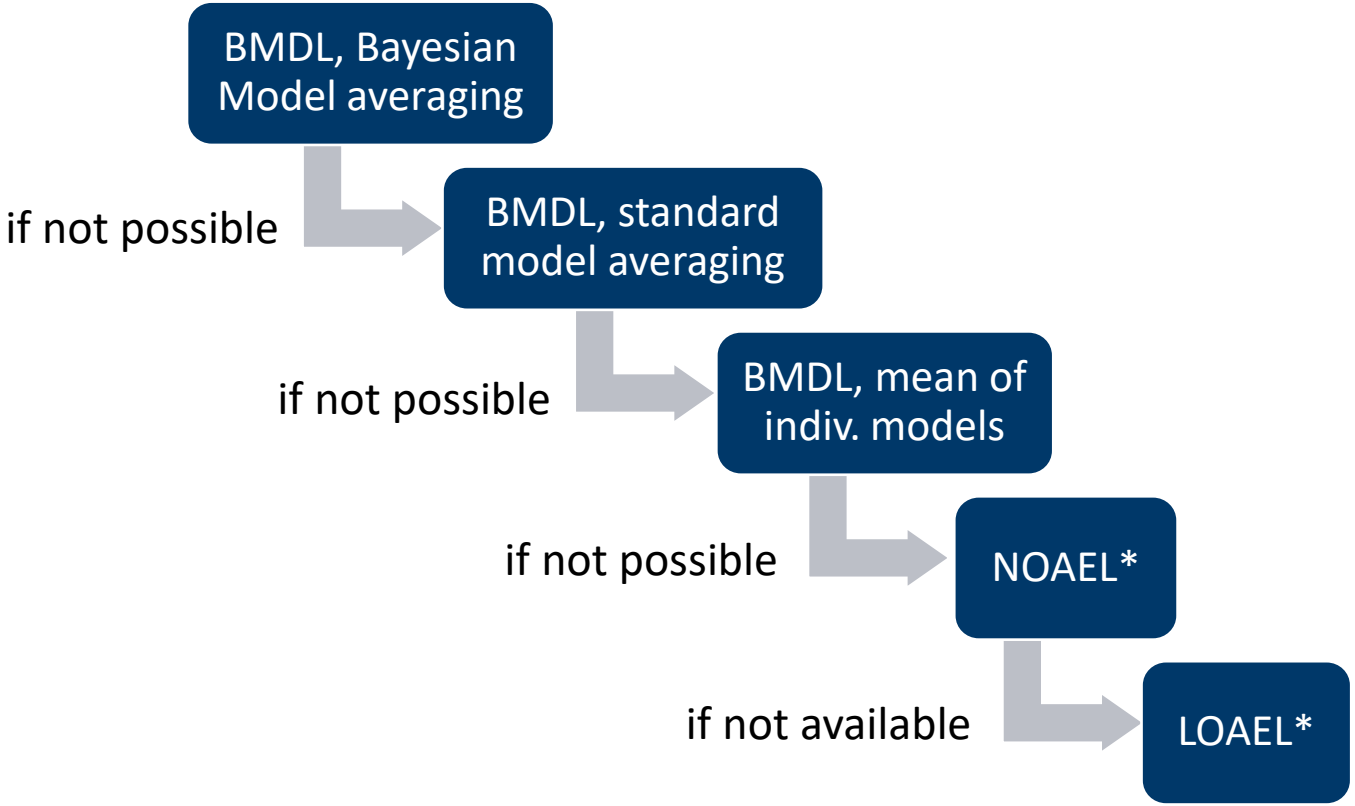

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Other HC aspects – two approaches run in parallel

„WHO approach“ (used for setting the TDI)

- Used for actual TDI derivation
- Using **default distributions** as per WHO IPCS (2018)

„BfR approach“

- Reliable **substance-specific data**, if available, were preferred over default assumptions
- **EFSA default AF**, if available, else: **REACH default AF** were assumed to **represent P95**
- More of an experimental approach to **investigate conservatism of WHO approach vs. using regulatory defaults**, needs further refinement

TDI calculation for all accepted studies

(deterministic and approximate probabilistic)

Reproductive toxicity

***Table 8**: Results of the deterministic and approximate probabilistic quantitative TDI derivation and uncertainty analyses. Studies are only listed of their PoD was either a BMDL, a LOAEL or a NOAEL that was not the highest dose tested. Overall Assessment Factors (OAF) are dimensionless, all other values are in µg/kg bw/d. PoDs > 1 OAFs and TDIs are rounded to integers and all other numbers are rounded to the first significant figure, unless the rounding error would exceed 10 %, in which case they were rounded to the second significant figure[7]. Values used for the hazard assessment are printed bold.*

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Sperm count															
(Delclos et al., 2014)	1	rat	SD	caudal count (no outliers)	764	BMDL	1	2	6.14	307	**2**	**48**	17176	**3**	698
(Wang et al., 2014a)	2	rat	SD	caudal count	7310	BMDL	1	6	6.14	921	**8**	**442**	**552109**	**12**	**8937**
(Liu et al., 2013a)	2	rat	Wistar	caudal count	26	BMDL	1	2	6.14	307	**0.09**	**2**	954	**0.14**	39
(Srivastava and Gupta, 2018)	2	rat	Wistar	caudal count	50	NOAEL	1	2	6.14	307	**0.16**	**3**	1873	**0.2**	78
(Tyl et al., 2002)	2	rat	SD	epididymal count, F1	136602	BMDL	1	2	6.14	307	**445**	**7762**	2.6E06	**511**	104039
(Tyl et al., 2008b)	2	mouse	CD-1 (Swiss)	caudal count, F0	362761	BMDL	1	2	5.00	250	**1452**	**16789**	4.4E06	**1117**	176603
	2	mouse	CD-1 (Swiss)	caudal count, F1 retained	354442	BMDL	1	2	5.00	250	**1419**	**20121**	6E06	**1334**	228107
(Karabulut and Gulay, 2020)	2	rabbit	NZW	conc. in ejaculate	1364	BMDL	1	2	2.44	122	**11**	**119**	33871	**8**	1362

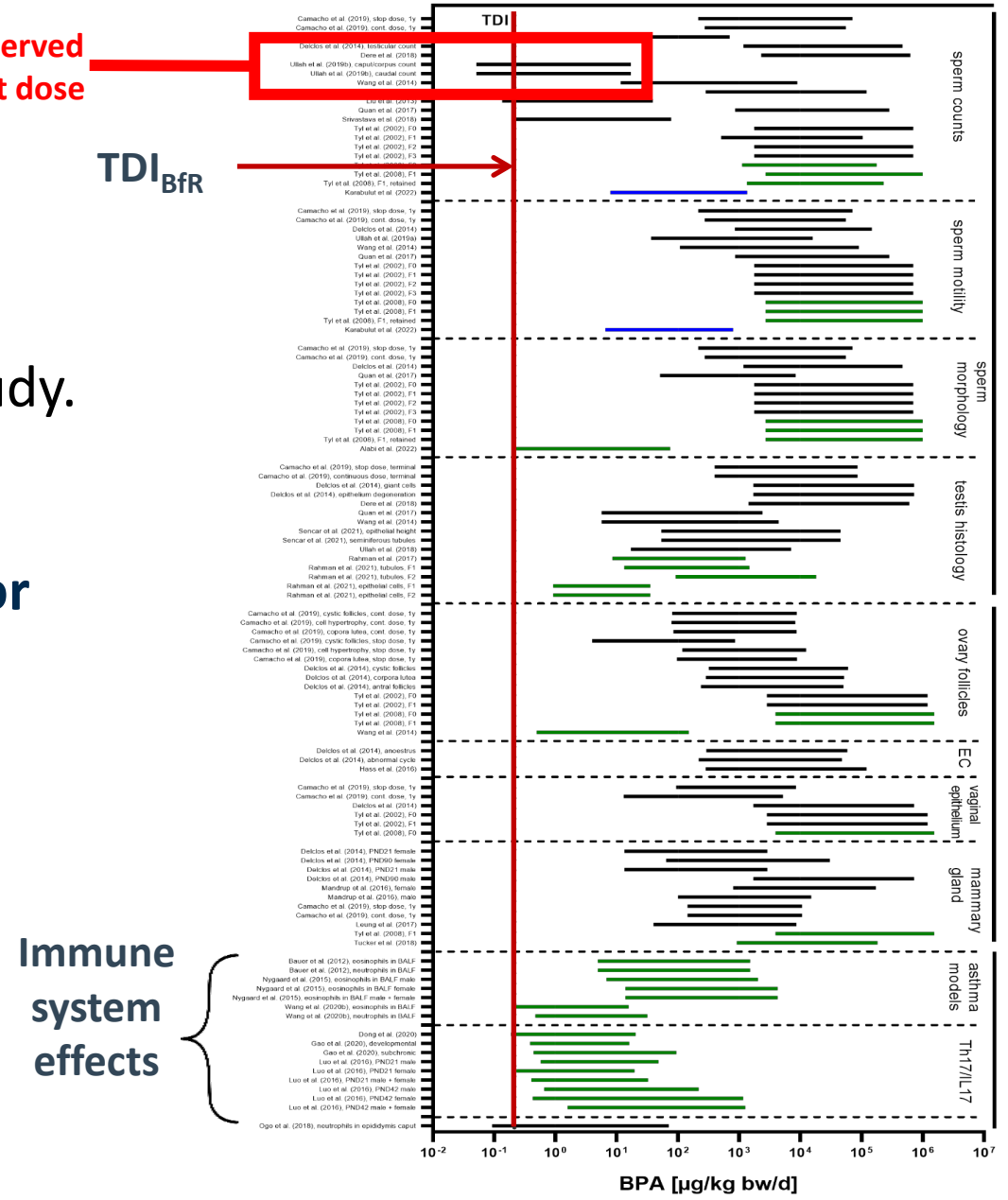
Overall TDI

TDI uncertainty ranges were determined by APROBA/WHO approach for each (admissible) study.
(protection of 99 % of the population with 95 % confidence)

Lowest lower bound of TDI uncertainty ranges for valid study results was taken as overall TDI.

BfR TDI would also mostly **cover immune effects** (but relevance questioned + other flaws).

WHO approach: TDI = 0.2 µg/kg bw/d
BfR approach: TDI = 2 µg/kg bw/d



Conclusions and Outlook

Applying the WHO approach in a data-rich setting was **easy and straightforward**.

Excellent way of assessing a large set of studies in a **consistent and transparent way**

Full risk assessment using exposure data from Spain is underway.

Cooperation with University of Granada, Spain, PhD thesis V. Ramírez Lopez, publication under prep.

APROBA should also be **explored for integrative use with NAMs, qAOPs, qST**.

Work on integrating probabilistic assessment into NGRA workflows has been initiated in EU research projects such as RISK-HUNT3R, ONTOX and PARC.

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