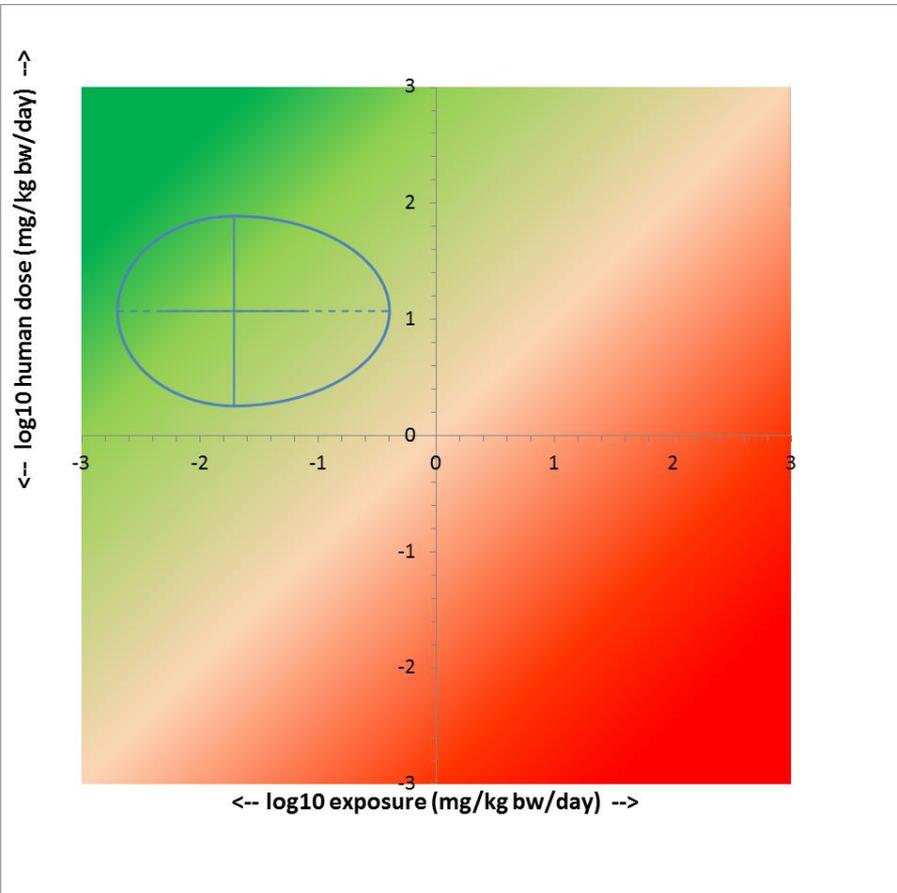




National Institute for Public Health  
and the Environment (RIVM)  
*Ministry of Health, Welfare and Sport*



Introduction to  
APROBA-Plus: A  
probabilistic tool to  
evaluate and express  
uncertainty in hazard  
characterization and  
exposure assessment  
of substances.

Bas Bokkers

International Conference on Uncertainty  
in Risk Analysis, 21-22 Febr. 2019

# Risk assessment



## Deterministic

- Risk not quantified (yes/no/maybe there's a risk)
- Assumed to be conservative, but unclear by how much. More conservative with more factors
- Contribution of sources of uncertainty not quantified
- Low information demand
- Fast

## APROBA-Plus

- Risk is not quantified (sens subpop. vs high exposed subpop.), but...
- ...level of conservatism can be set beforehand: RfD: exposure where (with **x%** confidence), **l%** of the population would be subject to less than **M%** decrease in RBC during a lifetime
- Quantifies rel. contribution of sources of uncertainty
- Low info demand
- Fast

## Probabilistic

- Pop. risk is quantified (x% of pop. has y% risk or increased response)
- Level of conservatism can be set:
  - Magnitude of effect
  - Incidence
  - Coverage (uncertainty)
- Quantifies rel. contribution of sources of uncertainty
- Detailed info required
- Time consuming



# APROBA-plus in a nutshell



- Hazard characterization

WHO tool: Approximate probabilistic analysis (APROBA)

- where uncertainty distributions are combined probabilistically,
- Results in  $HD_M^I$  distribution (and probabilistic RfD)

- Exposure assessment

- Addition of existing exposure info to APROBA (APROBA-plus)

- Graphical comparison of hazard and exposure assessment

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APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances

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## Guidance document on evaluating and expressing uncertainty in **hazard characterization**

"..... how uncertainties underlying a hazard characterization can be quantitatively evaluated and translated into an overall (again quantitative) statement on the uncertainty in the final outcome (e.g. a reference dose [RfD])."

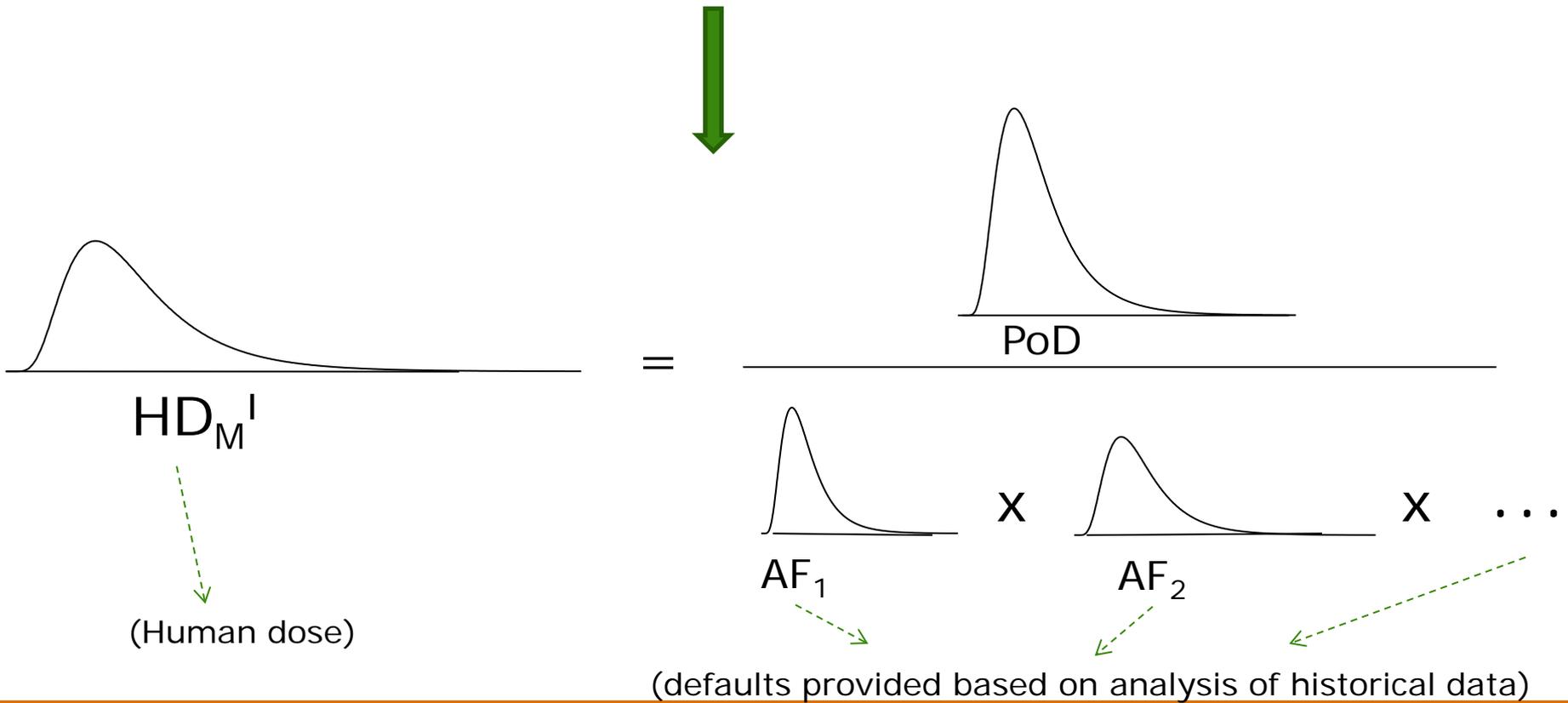
"The approach discussed should be viewed as an extension of existing approaches of hazard characterization and should not be seen as interfering with existing approaches."

# Conclusion of IPCS (1)



$$\text{RfD} = \frac{\text{PoD}}{\text{AF}_1 \times \text{AF}_2 \times \dots}$$

-----> (Point of departure)  
-----> (Assessment factor)



# Conclusion of IPCS (2)

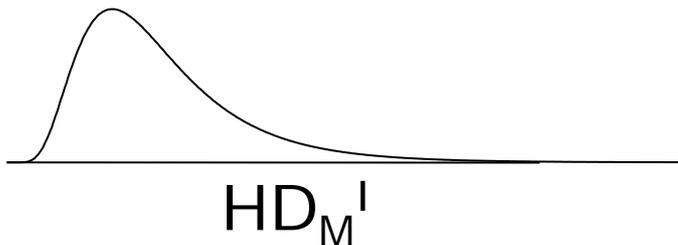


$HD_{M^I}$ :

dose at which only a small fraction ( $I$ , e.g. 1%) of the population will experience effects  $\geq M$

OR

dose where a large fraction ( $1-I$ ) of the population would be subject to a smaller than  $M$  effect.



**M:** magnitude of the effect

Some examples:

M = 5% decrease in RBCs

M = 10% AChE inhibition

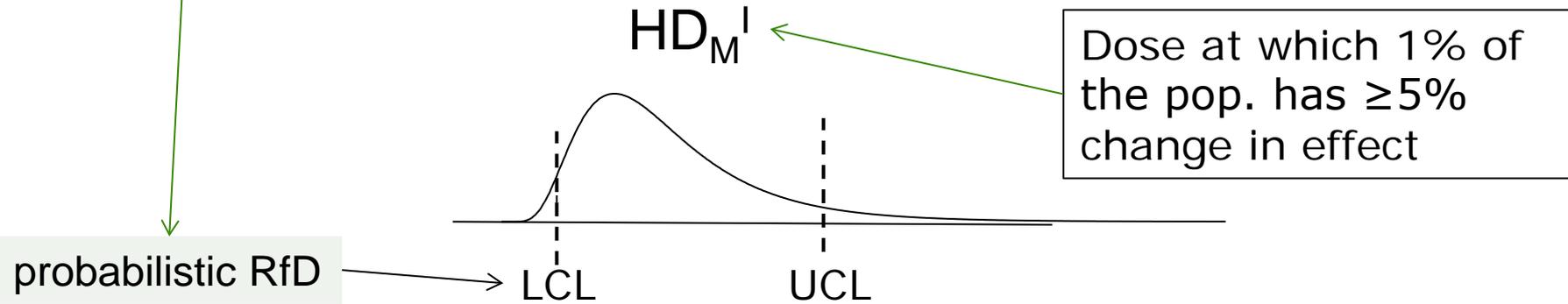
M = mild liver lesion

M = probability of getting cancer

# Results hazard characterization (1)



51	<b>APPROXIMATE PROBABILISTIC ANALYSIS OUTPUTS</b>			
52	<b>Standard Confidence Interval</b>			
53	<b>Target Human Dose (<math>HD_M^I</math>)</b>	<b>LCL (P05)</b>	<b>0.622</b>	<b>mg/kg bw/d</b>
54		<b>UCL (P95)</b>	<b>76.349</b>	<b>mg/kg bw/d</b>
55	<b>Degree of Uncertainty (Fold Range)</b>			
56	<b>Estimated "Coverage" of Deterministic RfD</b>			
57	<b>Probabilistic RfD</b>	= Approximate probabilistic $HD_M^I$ at specified % confidence		
58	<b>0.622</b>	= Estimate of dose (mg/kg bw/d) at which, with		
59		95%	confidence	
60		1%	of the population will have	<b>increased liver weight</b>
61		of magnitude	$\geq$	<b>5%</b>



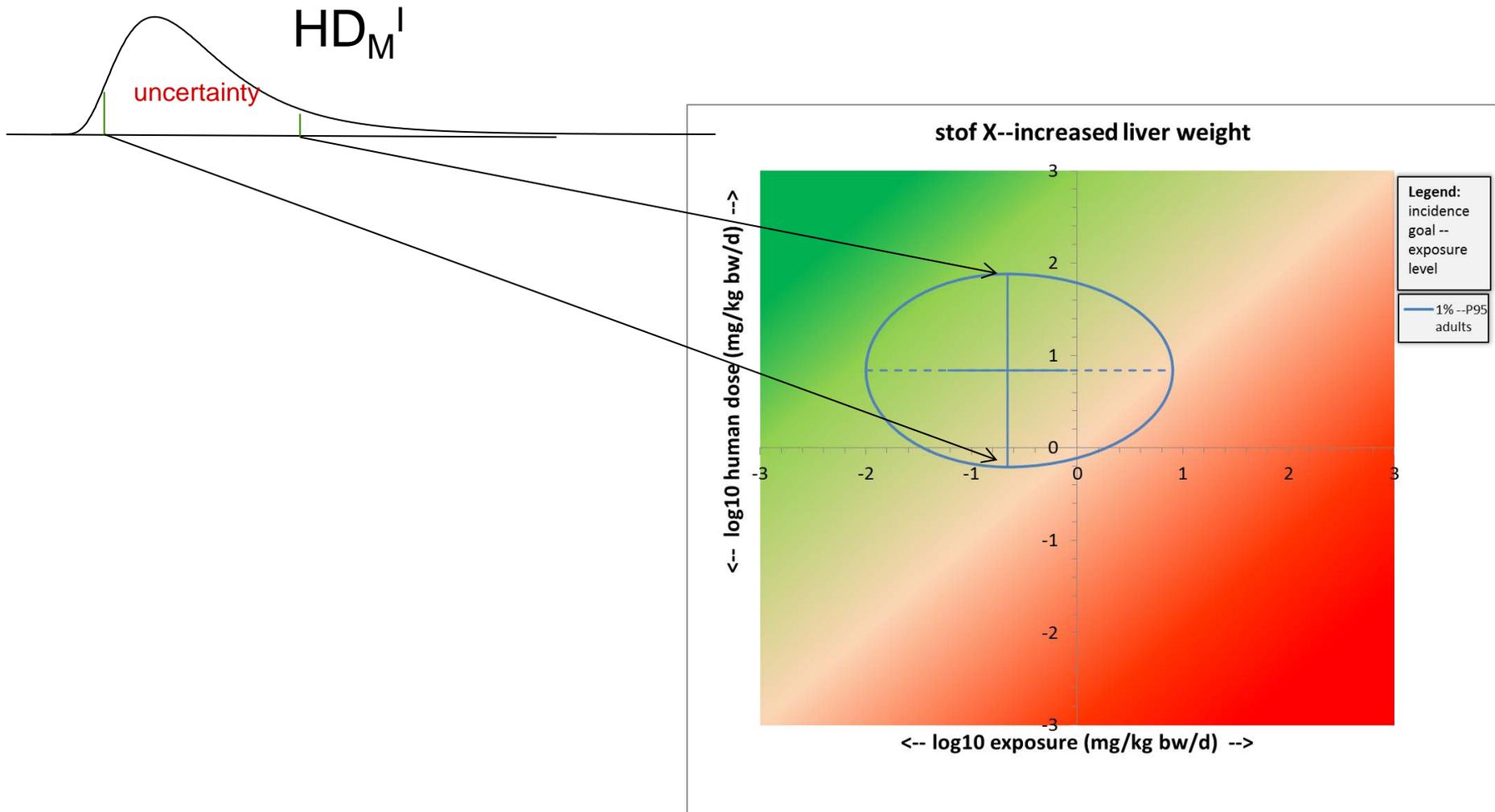
# Input exposure assessment



From externa source / outside APROBA-Plus

	A	B	C	D	E	F	G
1	<b>TITLE:</b>	stof X--increased liver weight					
2	<b>INPUTS RELATED TO EXPOSURE</b>						
3				enter available expo values, leave others empty			
4				Exposure unit:		mg/kg bw/d	
5				reported exposure		expert opinion on limits	
6	<b>DESCRIPTION</b>	<b>INPUTS*</b>		LCL	UCL	extra LCL	extra UCL
7							
8	exposure #1	P95 adults		0.0600	0.8000	0.0100	8.0000

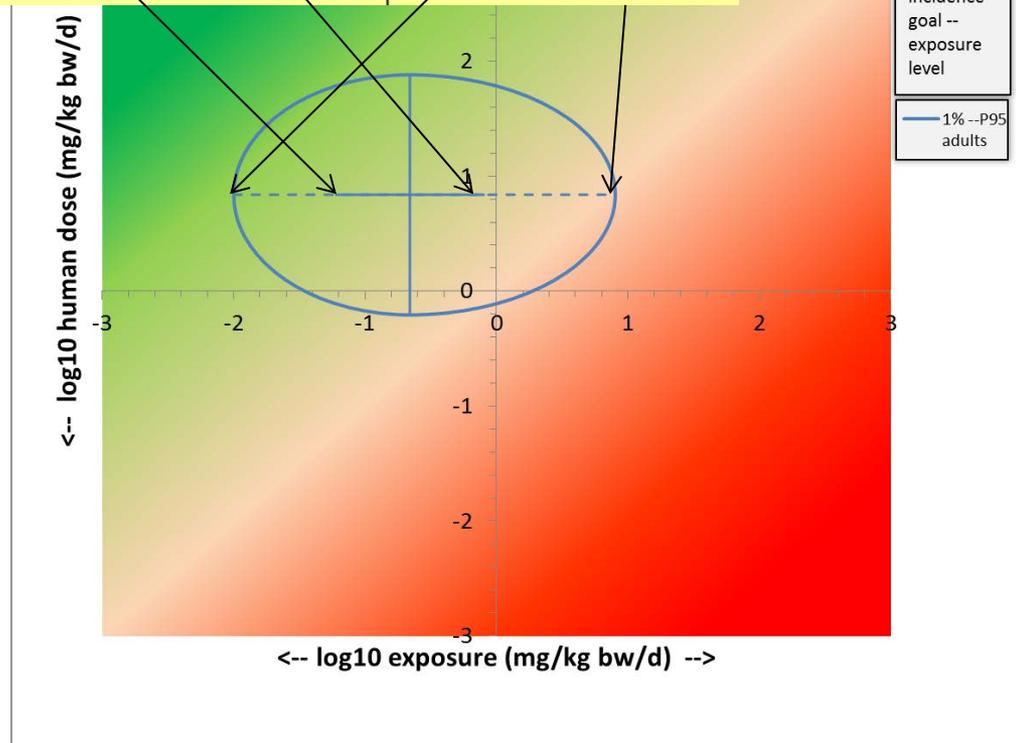
# Comparison hazard and exposure



# Comparison hazard and exposure



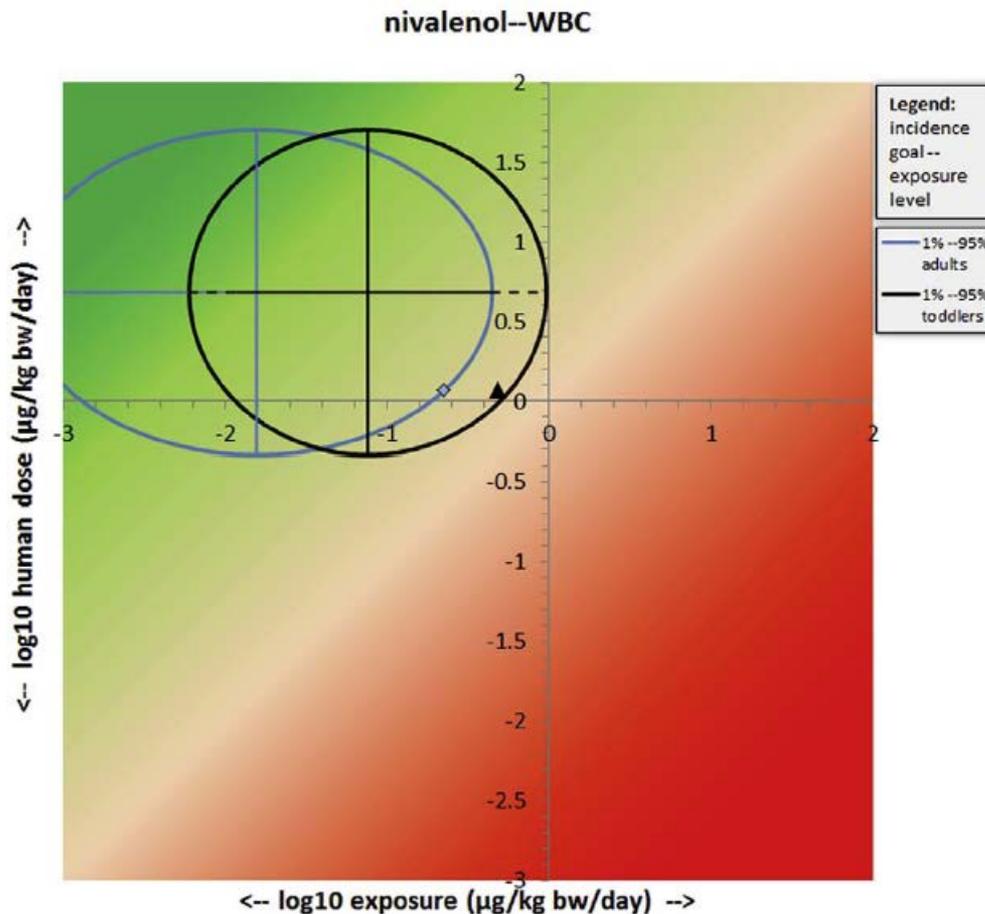
	A	B	C	D	E	F	G
1	<b>TITLE:</b>	stof X--increased liver weight					
2	<b>INPUTS RELATED TO EXPOSURE</b>						
3				enter available expo values, leave others empty			
4				Exposure unit: mg/kg bw/d			
5				reported exposure	expert opinion on limits		
6	<b>DESCRIPTION</b>	<b>INPUTS*</b>		LCL	UCL	extra LCL	extra UCL
7							
8	exposure #1	P95 adults		0.0600	0.8000	0.0100	8.0000



# Possible outcome, location (1)



- very likely that the protection goals (M and I) are met

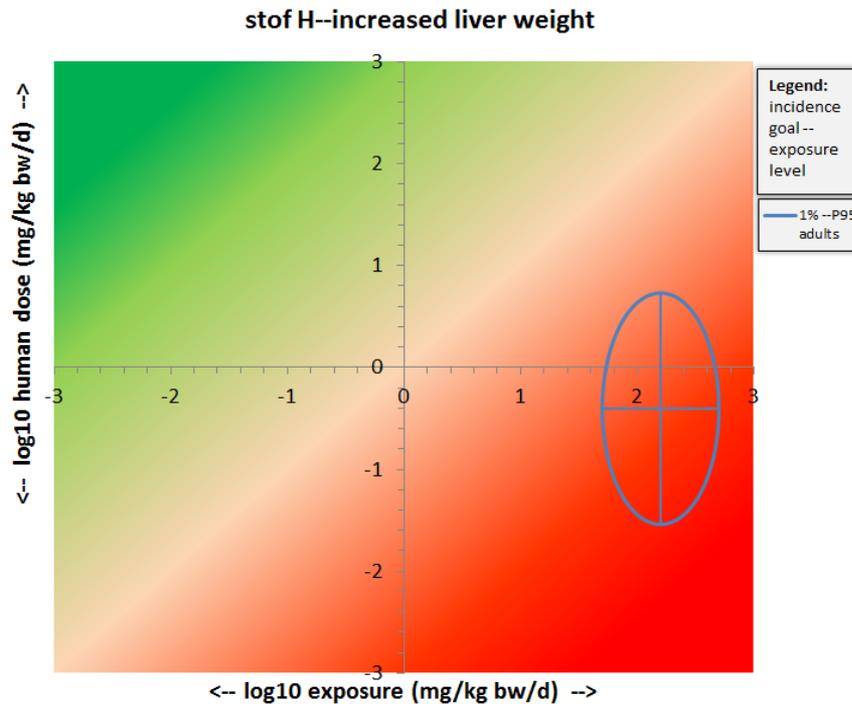


- Conclusive result
- No further action needed

# Possible outcome, location (2)



very likely that the protection goals (M and I) are not met

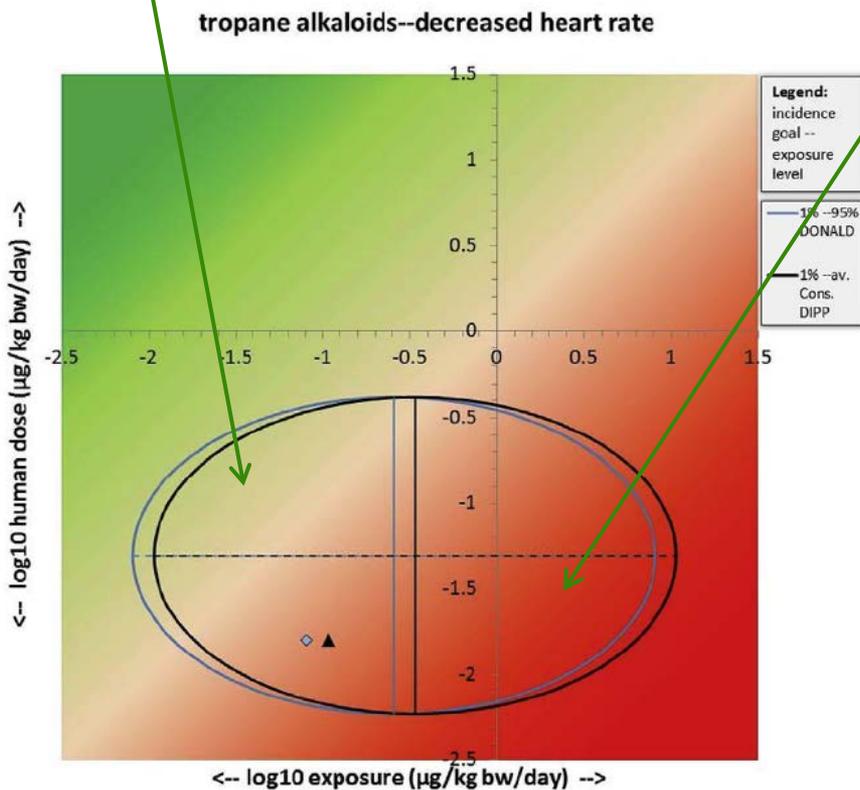


- Conclusive result
- Refining exposure or hazard assessment not useful
- Consider measures to reduce exposure

# Possible outcome, location (3a)



the odds are that the protection goals are not met, but it remains possible that they are

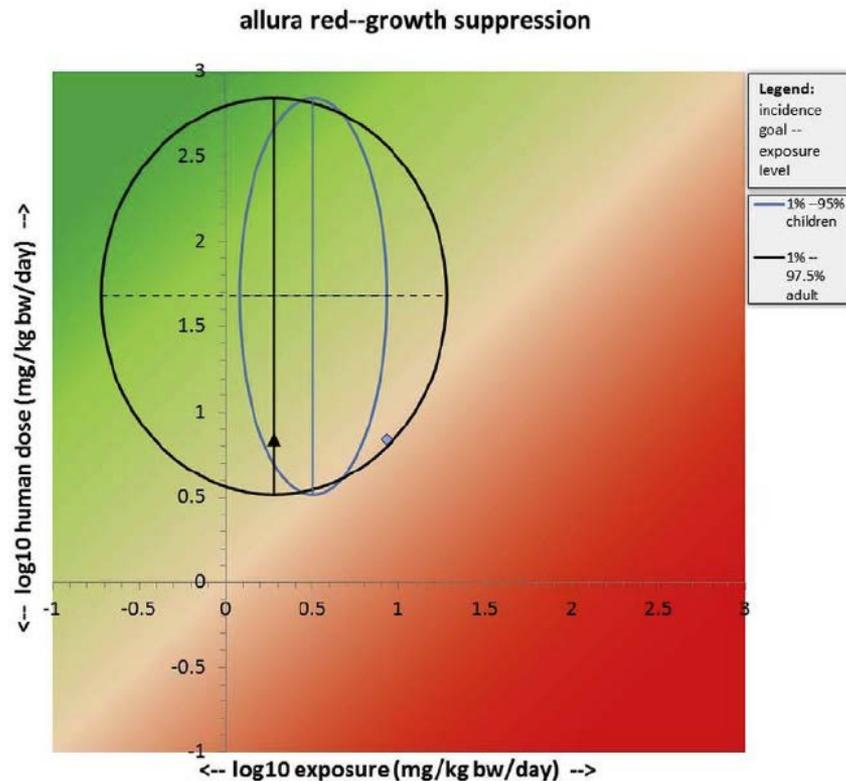


- Inconclusive result
  - Improve hazard assessment, e.g BMD analysis
  - Improve exposure assessment
- Or
- Full probabilistic RA

# Possible outcome, location (3b)



Small part of the uncertainty ellipse is located in (or close to) the red area. The odds are that the protection goals (M and I) are met, but it remains possible that they are not met

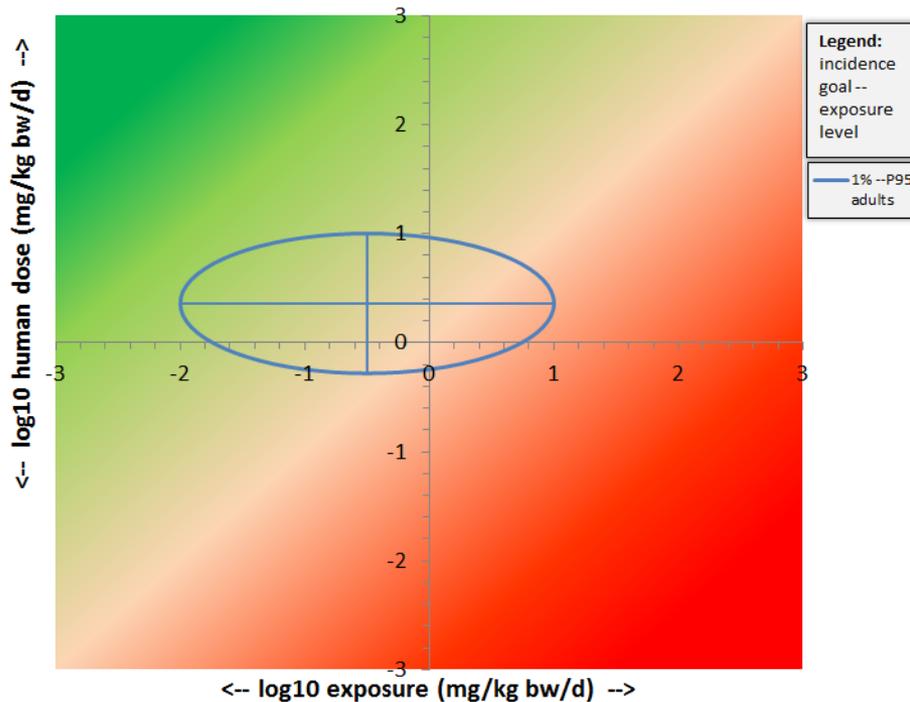


- Inconclusive result
  - Improve hazard assessment, e.g BMD analysis
  - Improve exposure assessment
- Or
- Full probabilistic RA

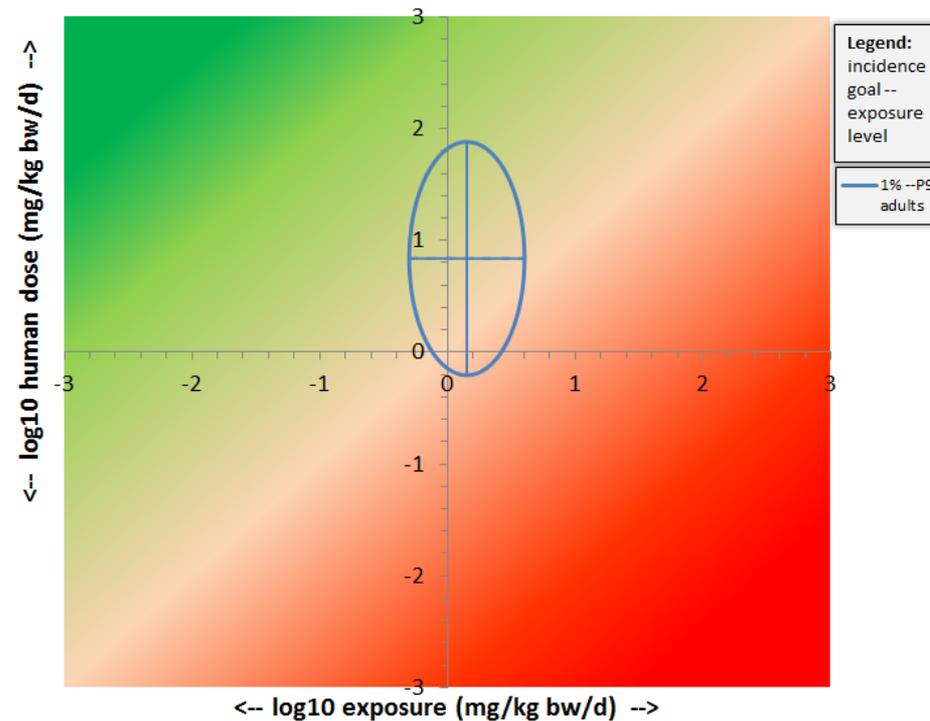
# Uncertainty, shape (1)



stof X--increased liver weight



stof X--increased liver weight

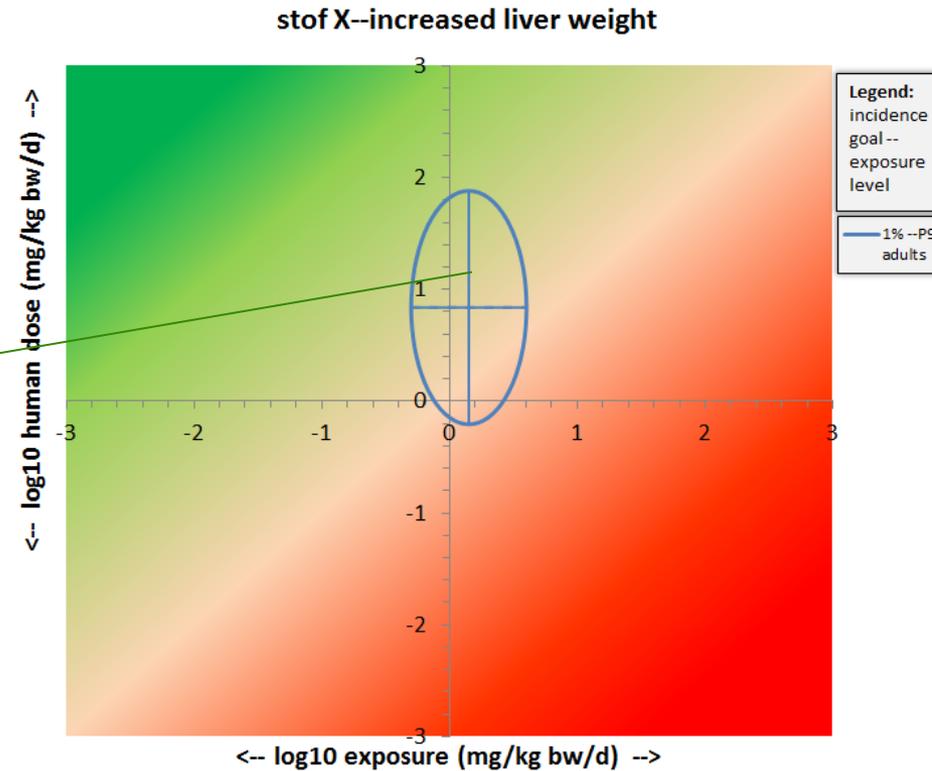


- Inconclusive result
  - Improve hazard assessment,
  - Improve exposure assessment

# Uncertainty, shape (2)



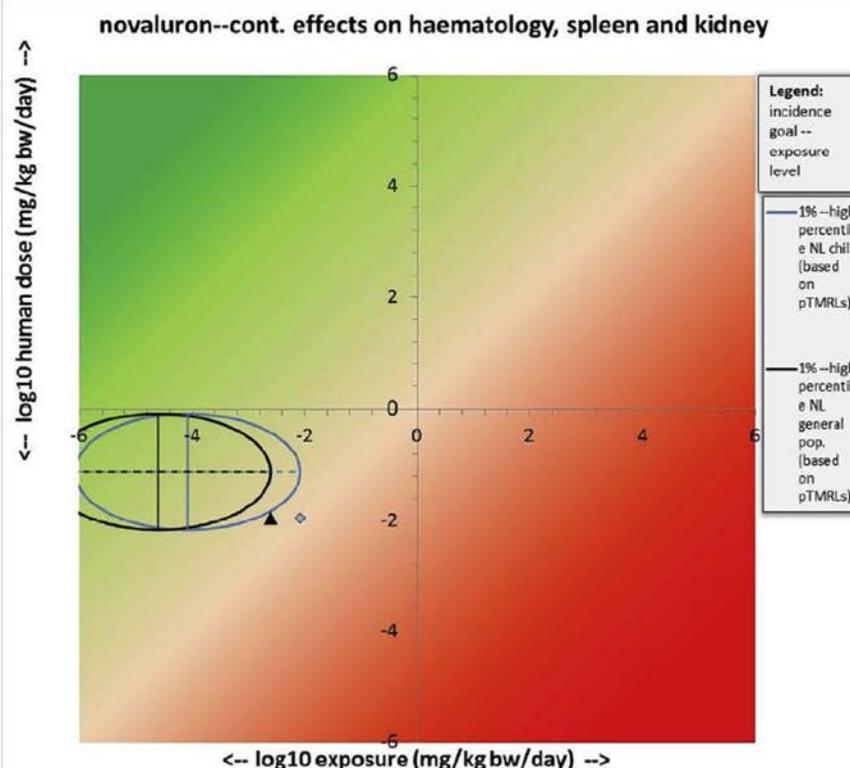
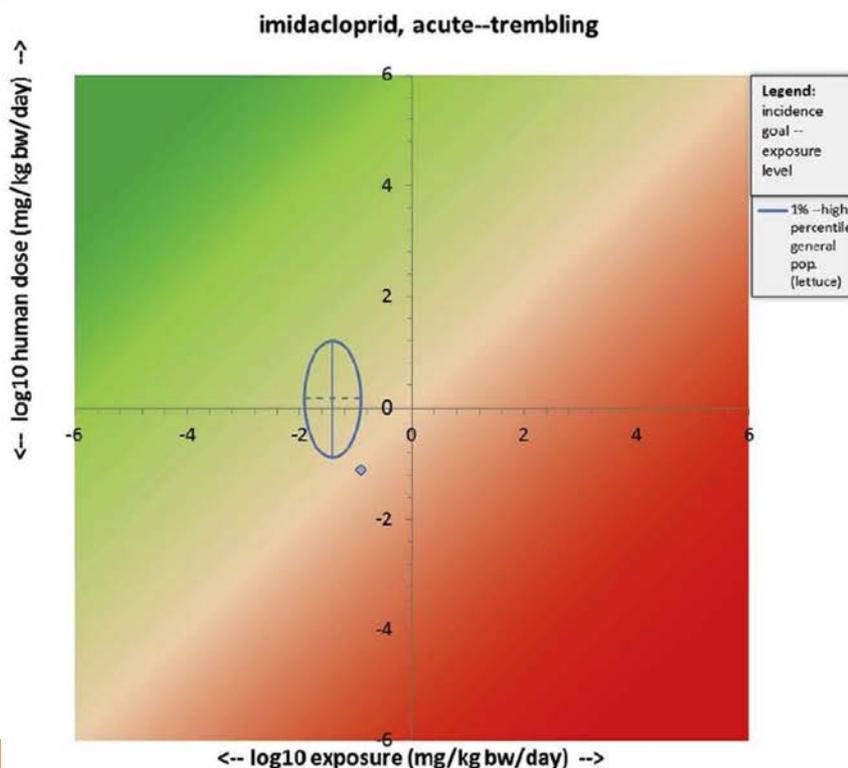
UNCERTAINTY ANALYSES ASPECT	% contribution to overall uncertainty
PoD	--
NOAEL to BMD	53%
Interspecies scaling	1%
Interspecies TK & TD <sup>2</sup>	17%
Duration extrapolation	--
Intraspecies	30%
toxicokinetics and toxicodynamics	



# Ranking



- (i) what fraction of the ellipse lies in the green/red area,
- (ii) how remote is the left upper part of the ellipse from the light-colored diagonal,
- (iii) how adverse is the effect associated with the PoD (i.e. the nature of the effect plus the value of M).



# Concluding remarks



- Visualizes risk and the uncertainty in exposure and hazard
  - Albeit in a sens. subpop. with high exposure
  - Informs follow-up / refinement
- Allows ranking
- Fast, when PoD (NOAEL or BMDL) and exposure are available (outside APROBA-Plus)
- APROBA-Plus is applicable for
  - oral, dermal, inhalation routes
  - subacute, subchronic, chronic, repro/developmental studies
  - All species
- Keep in mind uncertainties which are difficult to be quantified, e.g.
  - due to a complete lack of data
  - because we don't know how (all hazards captured?, study uncertainty)

# Further info



- 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.
- Chiu WA and Slob W (2015). A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. *Environ Health Perspect* **123**, 1241-54.
- Bokkers BGH, Mengelers MJ, Bakker MI, Chiu WA and 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.
- APROBA-Plus Excel tool:  
[https://www.researchgate.net/publication/326422432\\_APROBA\\_PLUS-V100\\_v012\\_TEMPLATE](https://www.researchgate.net/publication/326422432_APROBA_PLUS-V100_v012_TEMPLATE)
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- Marcel Mengelers (*RIVM*)
- Weihsueh Chiu (*Texas A&M*)
- Wout Slob (*RIVM*)

The End