L'évaluation des risques sanitaires face au challenge des relations dose-réponse non monotones

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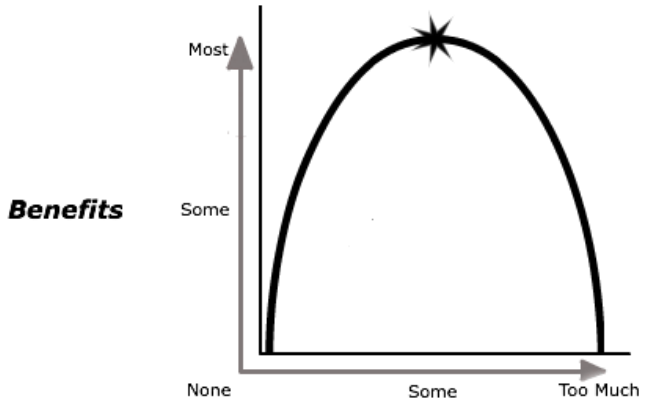
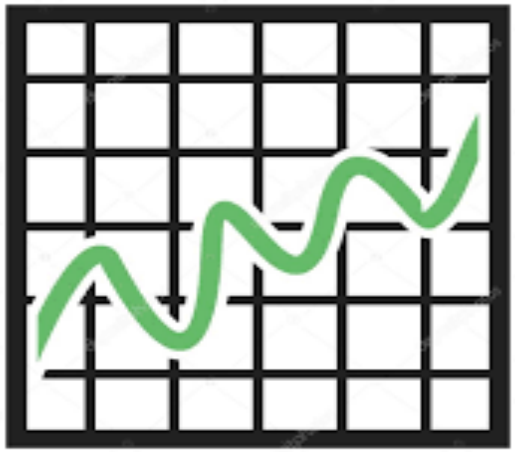
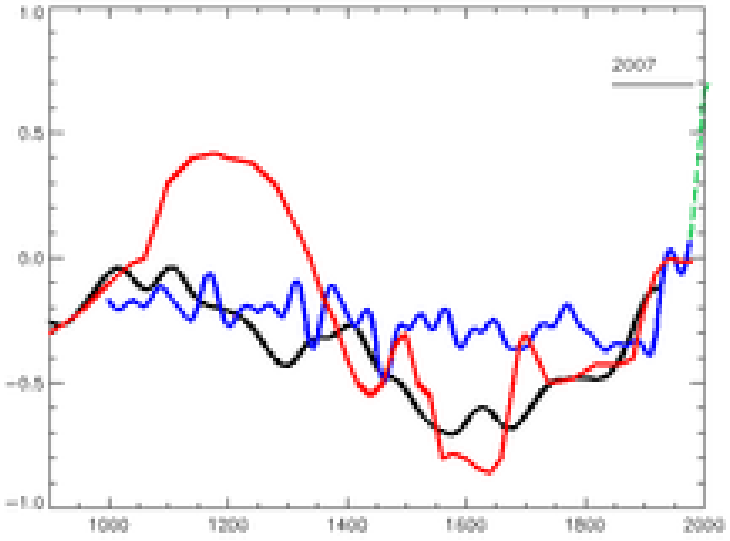
Amiens, 5 octobre 2017,

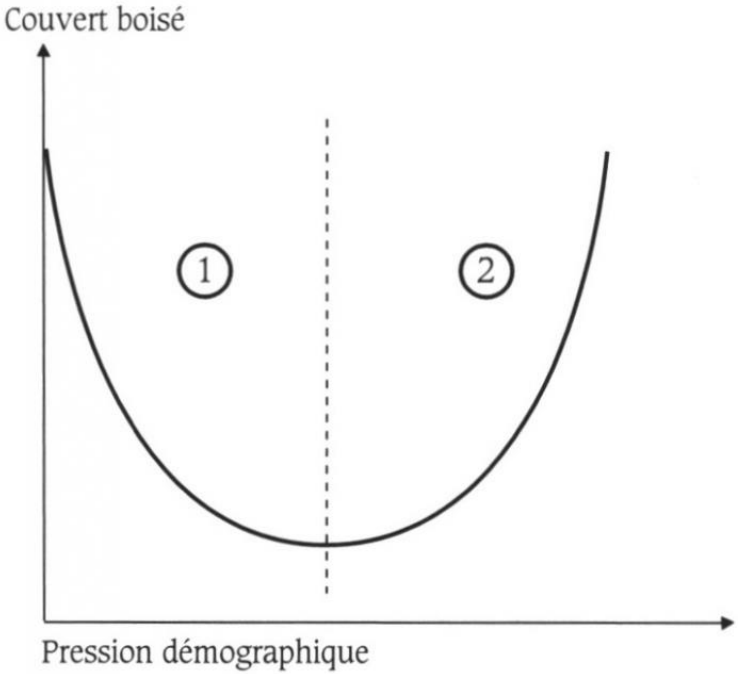
The Inverted U Curve





Anything

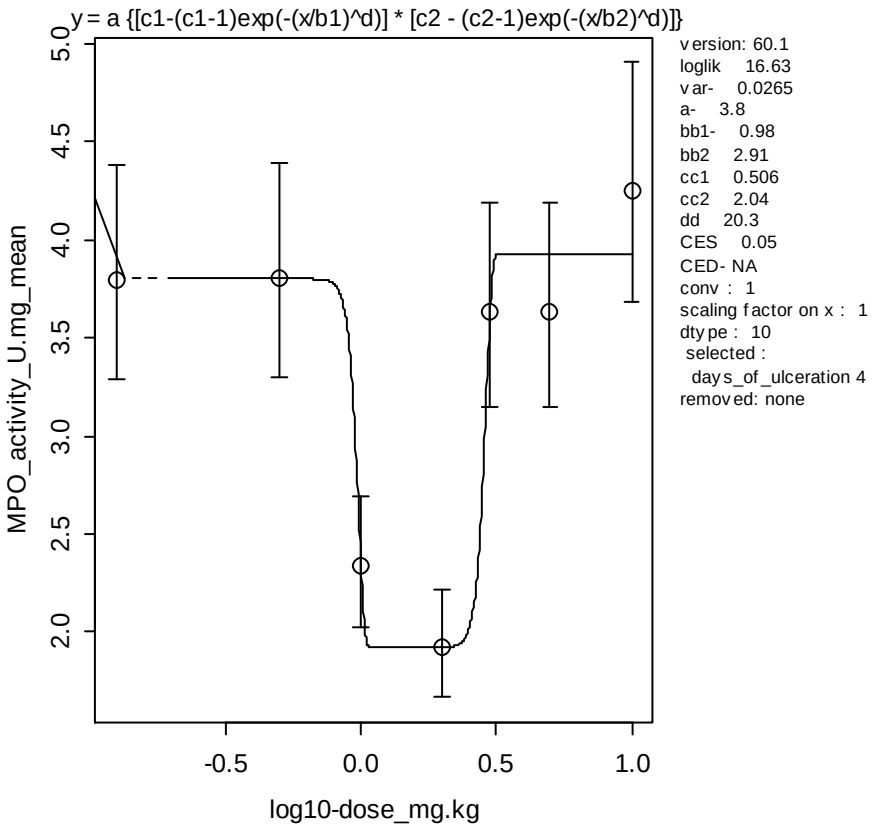


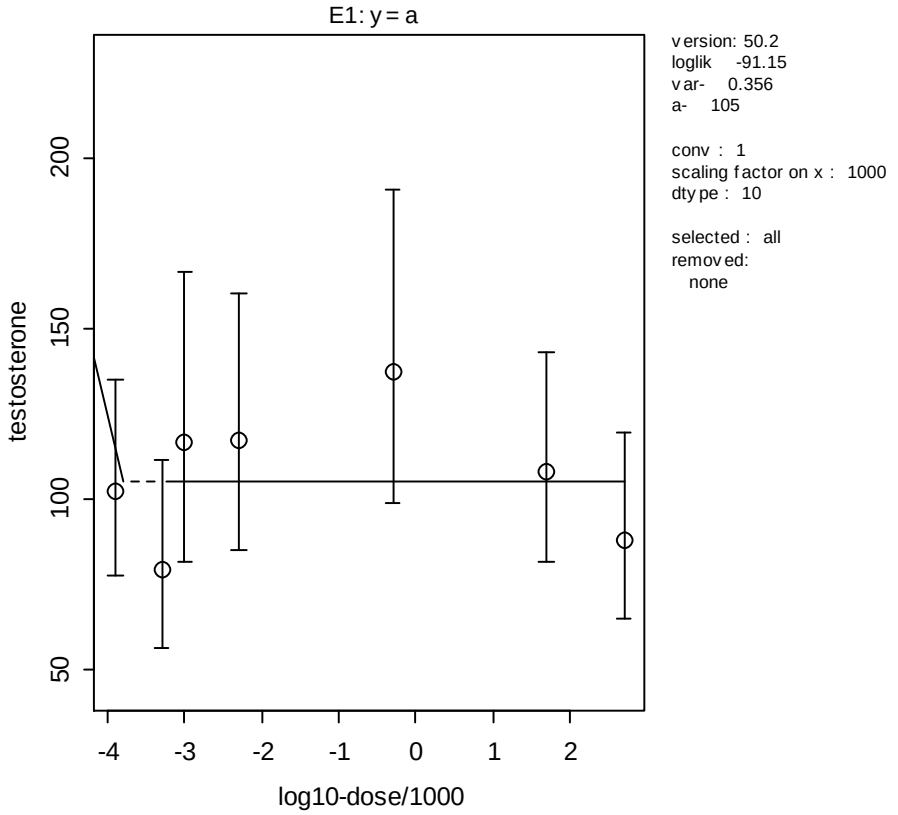


NMDR: Non Monotonic Dose Response Relationship

Definition of NMDR:

"Non-Monotonic Dose Response is defined as a function of dose in which the slope of the dose–response curve changes sign" (adapted from Vandenberg *et al.*, 2013).





Review of non-monotonic dose-responses of substances for human risk assessment GP/EFSA/SCER/2014/01

Corporate authors

Beausoleil C. [b], Beronius A. [c], Bodin L[b]., Bokkers, B.G.H. [d], Boon P.E. [d], Burger M. [a], Cao Y. [c], De Wit L. [d], Fischer A. [a], Hanberg A. [c], Leander K. [c], Litens-Karlsson S. [c], Rousselle C. [b], Slob W. [d], Varret C. [b], Wolterink G. [d], Zilliacus J. [c]

ED Workshop

22 May 2017

DTU Food/Copenhagen

Clémence VARRET &
NMDR Consortium Partners

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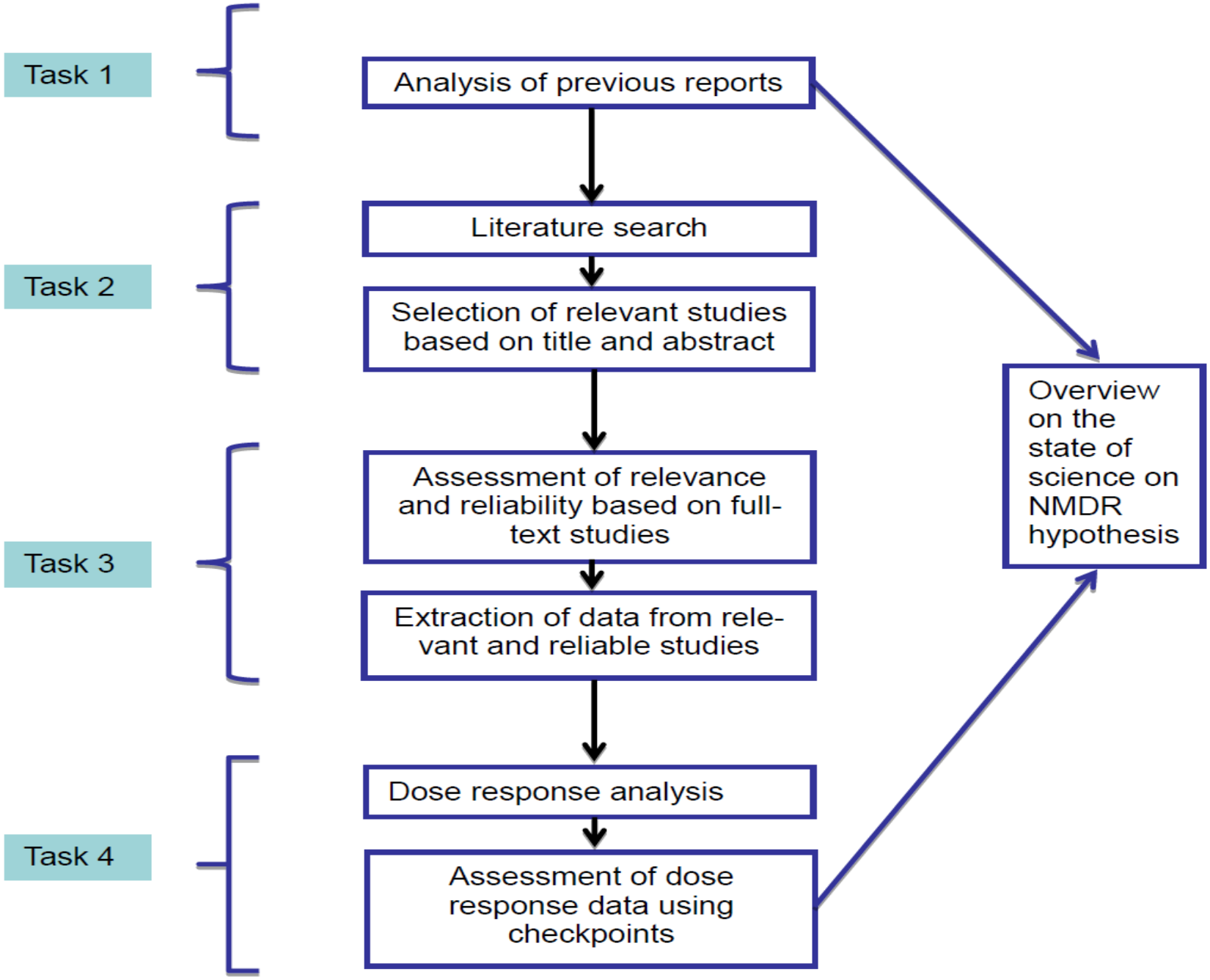
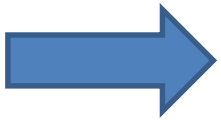
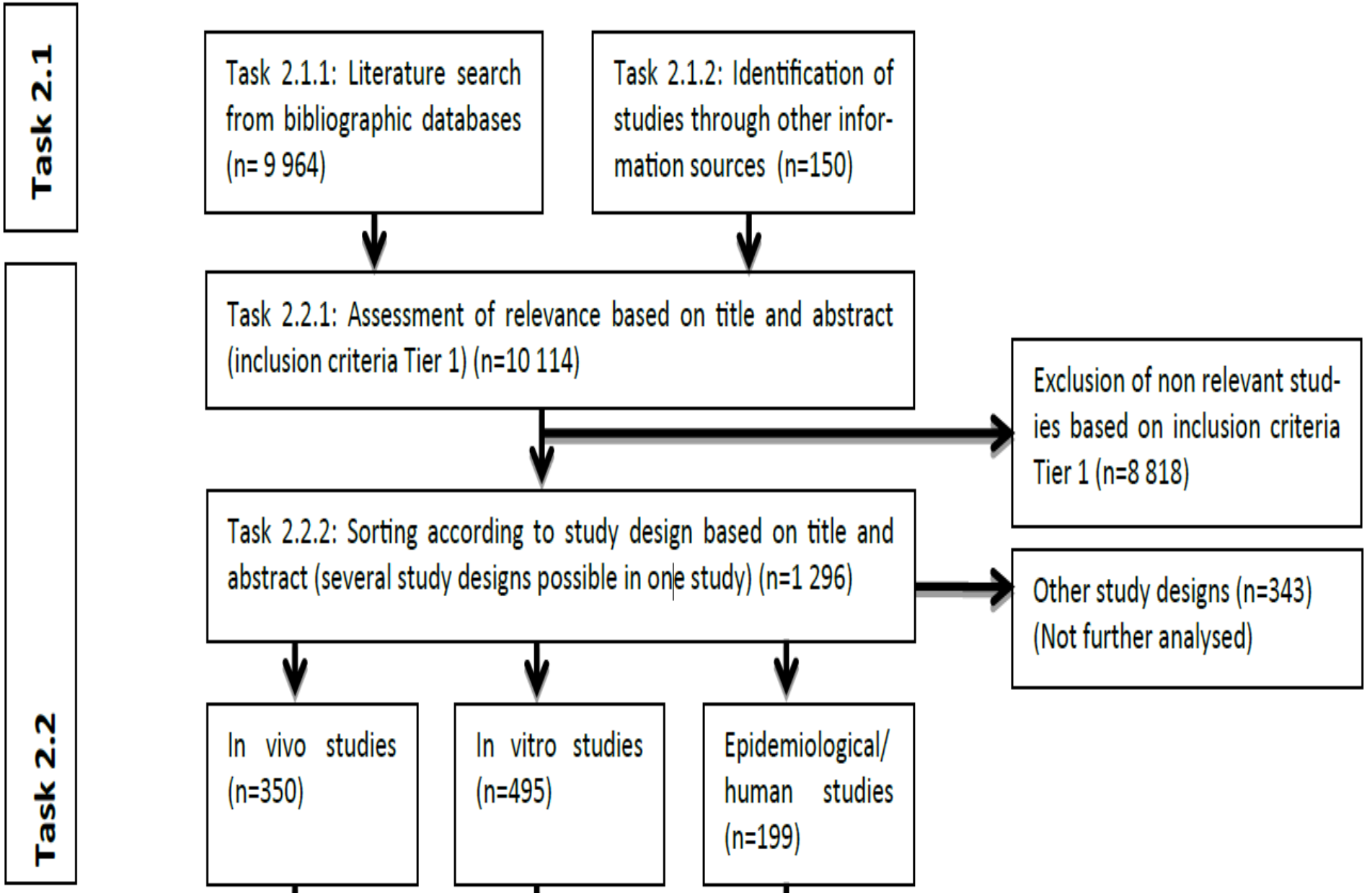

Task 1
Task 2
Task 3
Task 4
Analysis of previous reports
Literature search
Selection of relevant studies based on title and abstract
Assessment of relevance and reliability based on full-text studies
Extraction of data from relevant and reliable studies
Dose response analysis
Assessment of dose response data using checkpoints
Overview on the state of science on NMDR hypothesis

Methodology

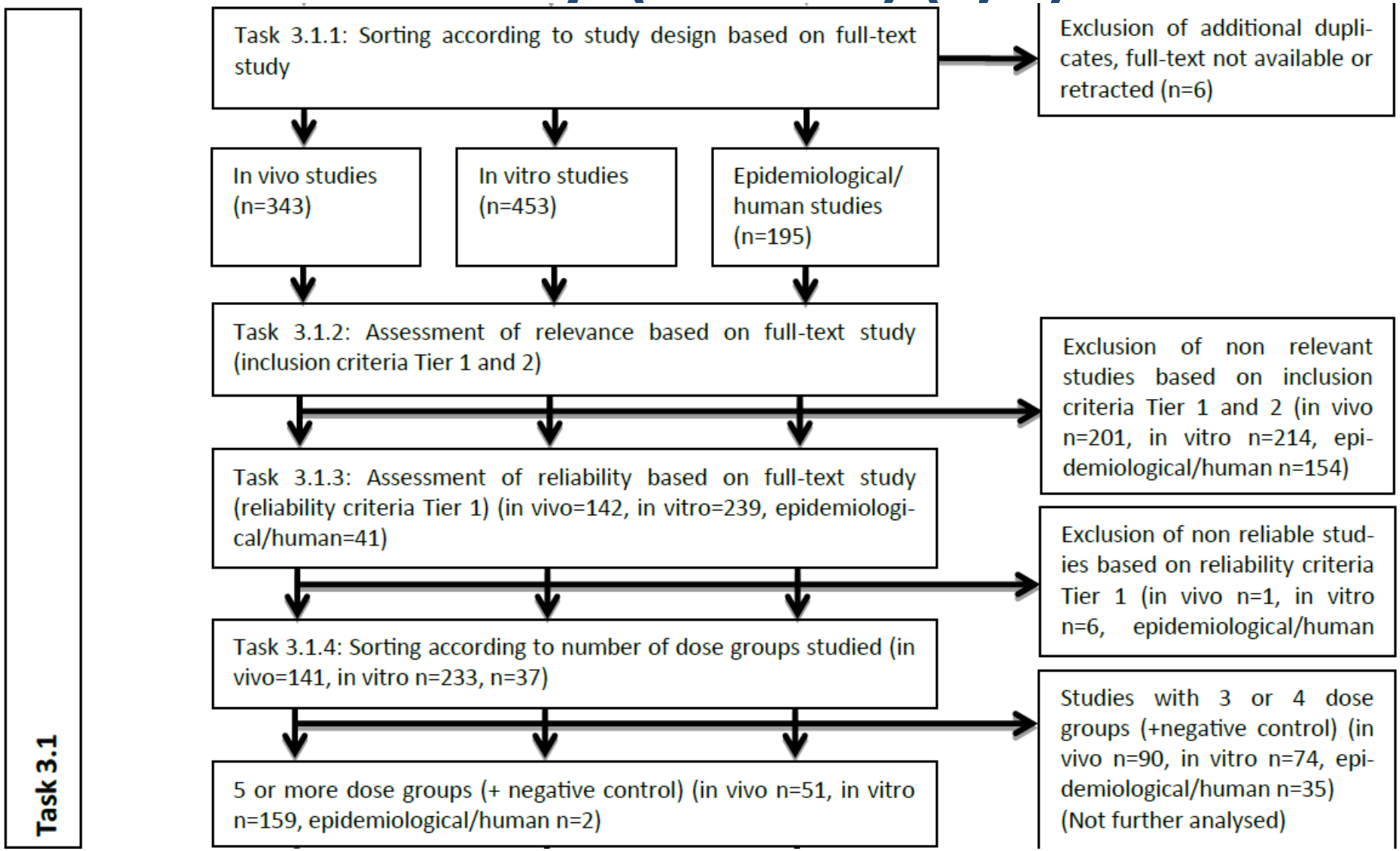
- **Systematic review methodology**
- **Inclusion criteria**
- **Assessment based on relevance & reliability**
- **Dose-response analysis:** Follow a dose-response analysis that compares non-monotone model with monotone model



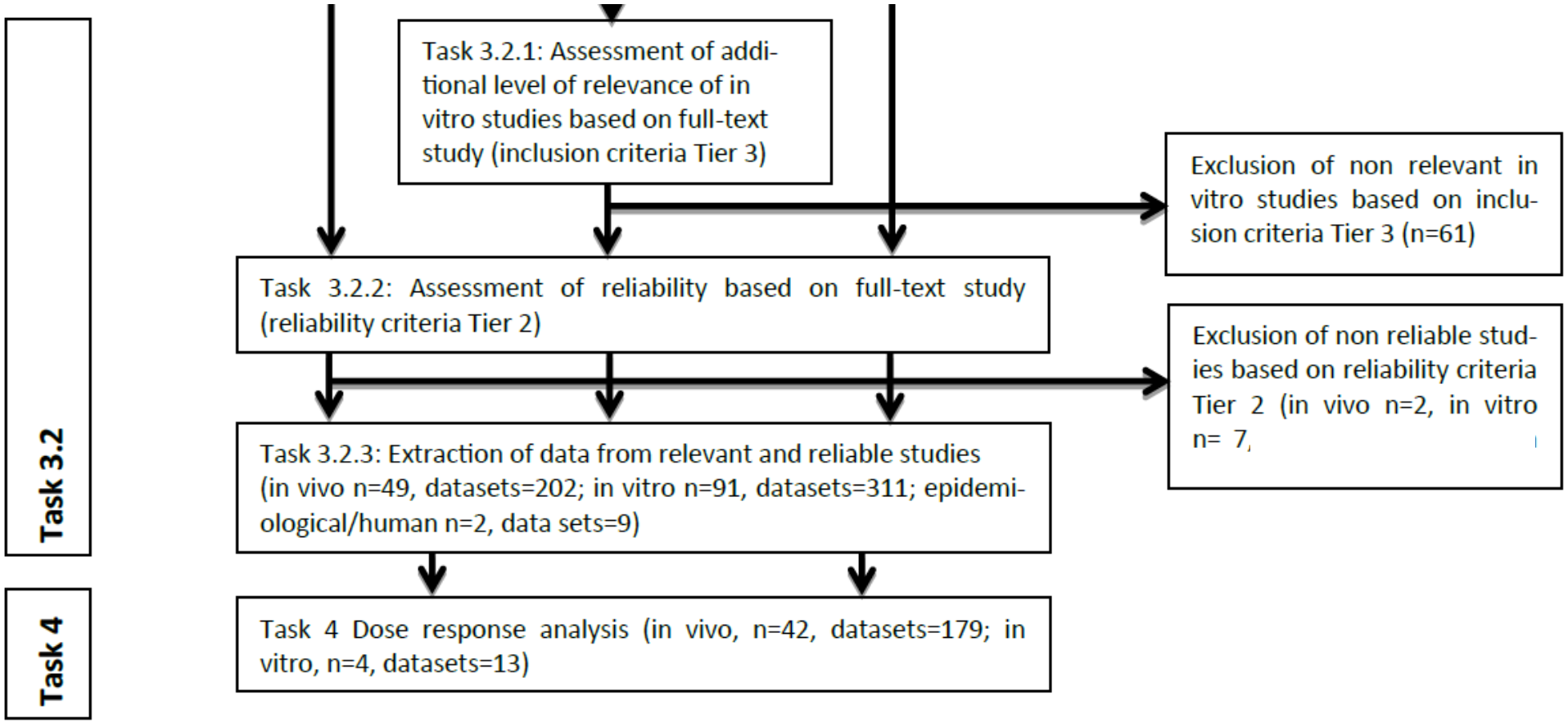
Development of a set of checkpoints


Task 2.1
Task 2.2
Task 2.1.1: Literature search from bibliographic databases (n= 9 964)
Task 2.1.2: Identification of studies through other information sources (n=150)
Task 2.2.1: Assessment of relevance based on title and abstract (inclusion criteria Tier 1) (n=10 114)
Exclusion of non relevant studies based on inclusion criteria Tier 1 (n=8 818)
Task 2.2.2: Sorting according to study design based on title and abstract (several study designs possible in one study) (n=1 296)
Other study designs (n=343) (Not further analysed)
In vivo studies (n=350)
In vitro studies (n=495)
Epidemiological/ human studies (n=199)

Task 3: assessment based on relevance & reliability (full text) (1/2)



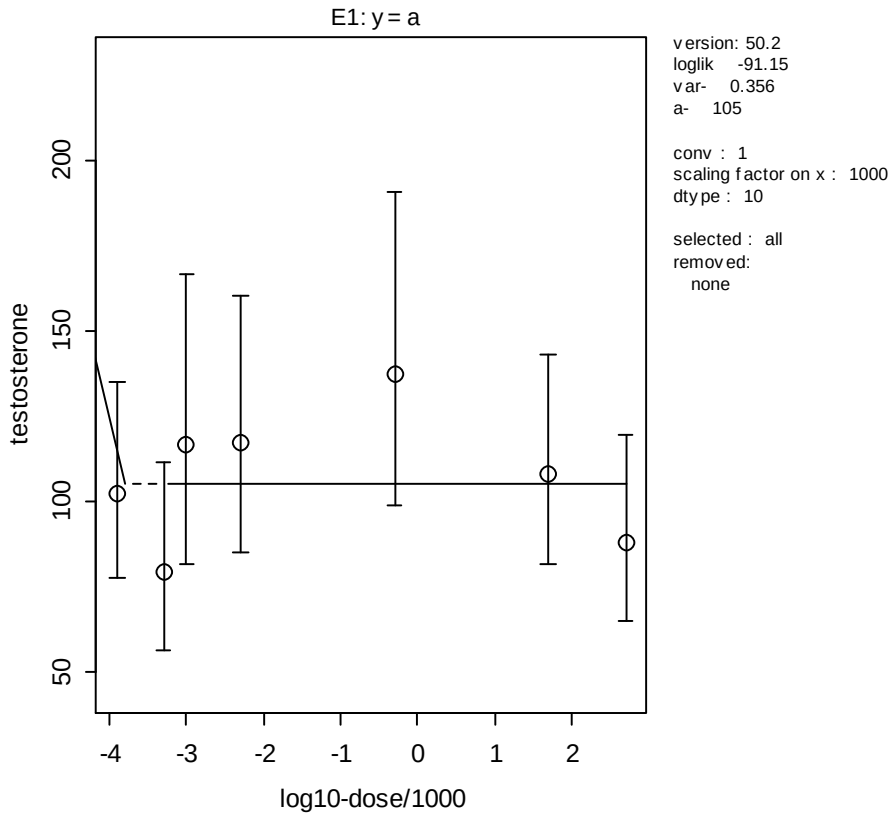
Task 3: assessment based on relevance & reliability (full text) (2/2)



Development of a set of checkpoints

- **Checkpoint 1**: Is there a dose-response?
- **Checkpoint 2**: Do one or both non-monotonic models fit the data better than a monotonic model?
- **Checkpoint 3**: Can the apparent NMDR be explained by one single potential outlying dose group?
- **Checkpoint 4**: Are the effect sizes in both directions of the NMDR greater than 5%?
- **Checkpoint 5**: Is the steepness of the dose-response curve outside the range of biologically plausible/realistic dose-response shapes?
- **Checkpoint 6**: Does the apparent NMDR consist of more (or less) than two directions ?

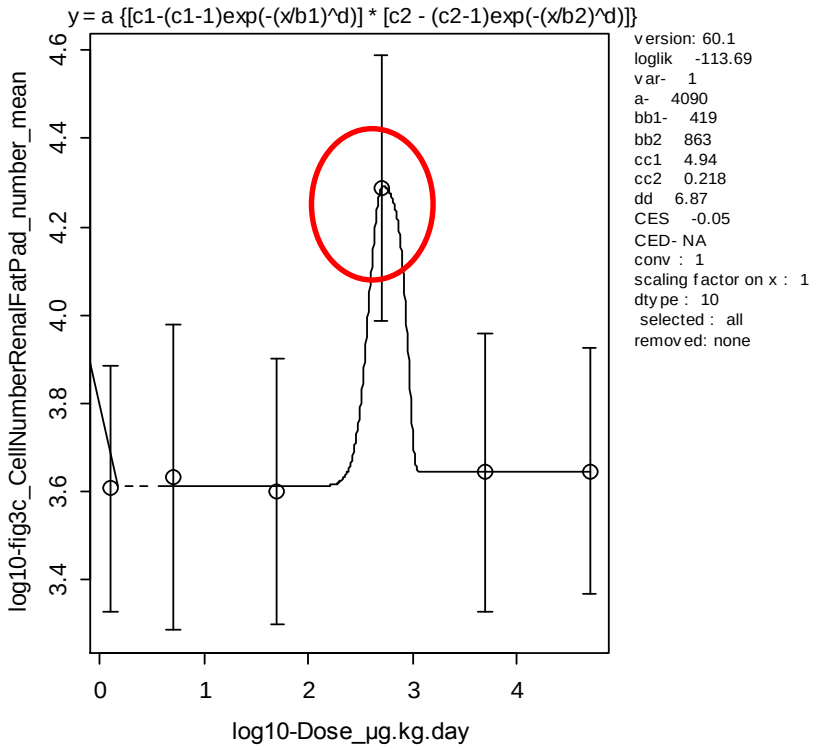
Checkpoint 1: Is there a dose-response?



Inspection of the plot with confidence intervals gives a similar answer as testing against the null model

Yes? CP fulfilled!

Checkpoint 3: could the apparent NMDR be due to more than a single outlier? Yes? CP fulfilled!



Examples where CP 3 is not fulfilled

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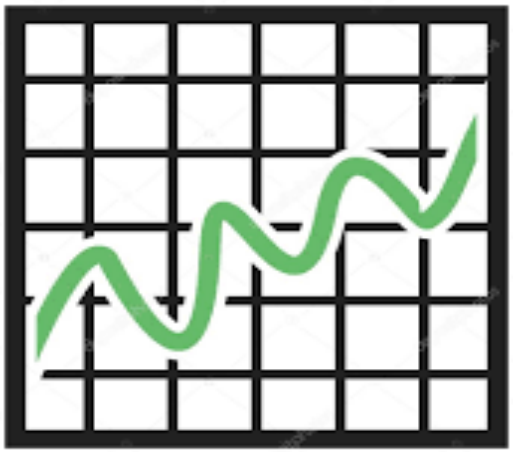
Results, discussion, recommendations



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Results *in vivo* (1)

Number of checkpoints (CPs) fulfilled

	DR analysis done	6	5	4	3	2	1	0
No of datasets (%)	179 (100)	11 (6)	36 (20)	30 (17)	29 (16)	19 (11)	43 (24)	11 (6)
No of studies	42	5	16	21	20	13	14	9

- 11 out of the 179 *in vivo* datasets fulfilled all 6 checkpoints
- 5 substances: quercetin, resveratrol, alpha-benzene hexachloride, DEHP and methyl-mercury
- Outcomes mainly at molecular/cellular level, one pathological - gastric ulcer index

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Results *in vivo* (2): CPs fulfilled

	DR analysis done	CP1	CP2	CP3	CP4	CP5	CP6
No of datasets (%)	179 (100)	145 (81)	88 (49)	33 (18)	132 (74)	65 (36)	71 (40)
No of studies	42	41	32	17	40	27	24

- In 82% of the datasets the apparent NMDR might have been caused by a single outlying dose group

Checkpoint 1: is there a DR?
Checkpoint 2: NM fits better than M?
Checkpoint 3: potential NM explained by one single potential outlying dose group?
Checkpoint 4: Are the effect sizes in both directions of the NMDR greater than 5%?
Checkpoint 5: Is the steepness outside the range of biologically plausible/realistic dose-response shapes?
Checkpoint 6: Does the apparent NMDR consist of more (or less) than two directions ?

Results *in vivo:* 6 CPs fulfilled (3)

Study	Test substance	Outcome/effect measured	Possible hormon-related mechanism of action	Number of dose levels tested
Bai 2010	**Quercetin**	Plasma concentration of PGE2	Not known	5
Dey 2009	**Resveratrol**	Stomach ulcer index (damage score) after 3 day of ulceration	Not known	6
Dey 2009	**Resveratrol**	Myeloperoxidase (MPO) activity (2 day)	Not known	6
Dey 2009	**Resveratrol**	Myeloperoxidase (MPO) activity (7 day)	Not known	6
Dey 2009	**Resveratrol**	Myeloperoxidase (MPO) activity (10 day)	Not known	6
Andrade 2006*	**DEHP**	Hypothalamic/preoptic area aromatase activity (male rats at PND 1)	Estrogen, androgen	10
Puatanachokchai 2006	**Alpha-benzene hexachloride**	Proliferating cell nuclear antigen (PCNA) in GST-P positive foci in liver	Not known	6
Puatanachokchai 2006	**Alpha-benzene hexachloride**	NADPH-P450 reductase activity in liver	Not known	6
Puatanachokchai 2006	**Alpha-benzene hexachloride**	8-hydroxydeoxyguanosine (8-OHdG) formation in liver	Not known	6
Puatanachokchai 2006	**Alpha-benzene hexachloride**	2α-testosterone hydroxylase activity in liver	Estrogen, androgen	6
Zhang 2013	**MeHg**	GRP78 protein expression in the cerebral cortex	Not known	5

*Developmental/prenatal exposure

5 checkpoints fulfilled

(36 datasets from 16 studies)

Substances
Acetaldehyde
Acrylonitrile
Alpha-benzene hexachloride
Caffeine
DDT
Ethanol
Lead acetate (Pb(II))
Myricetin
Resveratrol
Rosmarinic acid
Tanshinone IIA
Triclosan

Outcome/effect
16 α-testosterone hydroxylase activity in liver
Brain AChE activity
Change in body weight
CYP450 content in liver
Freezing behavior of mice exposed to conditioned fear stress
Frequency of play fighting
Frequency of social investigation
GST-P positive foci in liver
Lipid peroxidation in the cerebrum
Locomotor activity
mRNA expression of IL-1 receptor type 1
mRNA expression of TNF-alpha receptor type 1
Myeloperoxidase (MPO) activity in stomach ulcer
Plasma PGE2
Pulse pressure
Seizure
Total horizontal activity
Total serum T3
Total travelled distance
Ulcer index

Conclusion

- At least 5 doses + 1 control needed
- We propose a set of 6 checkpoints as tool for evaluating the evidence of NMDR
  - taking into account that data always contain both random and non-random sampling errors
- For most datasets the empirical evidence for NMDR was limited (6 CPs fulfilled)
- If 6 CPs fulfilled: not a straight conclusion, but requires an independant study to reproduce the results

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How to use these data for Risk Assessment?

- Uncertainty can be divided in 2 groups:
  - Uncertainty that could be reduced if more data become available :
    - LOAEL *versus* NOAEL
    - All windows of exposure not covered

    Apply specific usual UFs
  - UF that have low plausibility to be reduced even with more data
    - Limited endpoints assessed (that may occur at lower dose)
    - Late effects
    - **Possibility of NMDR**

    Apply a global ED UF: which value ?

In addition to the « usual » UFS apply a 10 or 100 default UF

How to use these data for Risk Assessment

- If NMDR claimed by the authors: apply checkpoints to check
- If NMDR confirmed in one study: compare with other on the same compounds/endpoints
- If NMDR plausible then:
  - Consider only the monotonic part of the curve in the range of dose corresponding to the exposure situation

Or

  - Take the lowest "NOAEL" (and apply an uncertainty factor!)

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https://www.efsa.europa.eu/en/press/news/160503

Update on non-monotonic dose response

July 2014 to December 2015

efsa
European Food Safety Authority

A new EFSA external scientific report is "a useful contribution to the scientific debate" on non-monotonic dose response (NMDR) results from toxicity studies, according to Prof Anthony Hardy, Chair of EFSA's Scientific Committee. "More analysis and discussion are needed to prepare for a comprehensive assessment of the evidence for non-monotonicity," he stated.

3 May 2016

Merci pour votre attention!

Questions?

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