Data requirements for natural substances: putting in place a tiered approach

An Vanden Bosch

ABIM conference, Basel, 22 October 2019

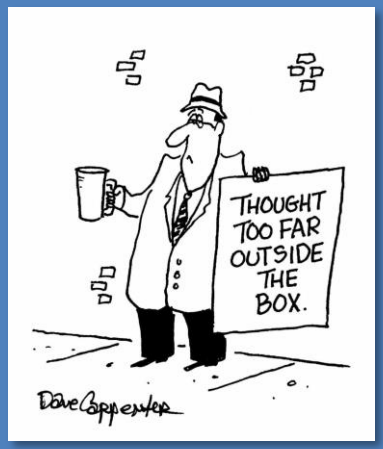
Striking the balance

other regulatory frameworks

other study designs

‘thinking out of the box’

‘thinking too far out of the box’



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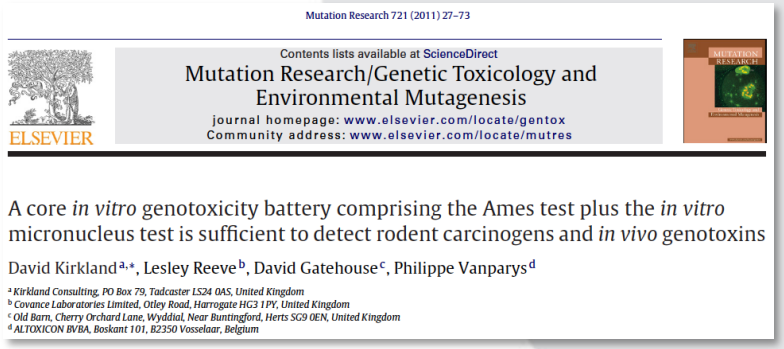
genotox / (sub)chronic tox / degradation

Data requirements for genotoxicity


Mutation Research 721 (2011) 27–73

Contents lists available at ScienceDirect

Mutation Research/Genetic Toxicology and Environmental Mutagenesis

journal homepage: www.elsevier.com/locate/gentox

Community address: www.elsevier.com/locate/mutres

A core *in vitro* genotoxicity battery comprising the Ames test plus the *in vitro* micronucleus test is sufficient to detect rodent carcinogens and *in vivo* genotoxins

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[b] Covance Laboratories Limited, Otley Road, Harrogate HG3 1PY, United Kingdom
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Food and Chemical Toxicology 106 (2017) 600–608

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

In vitro genotoxicity testing—Can the performance be enhanced?

Raffaella Corvi*, Federica Madia

European Commission, Joint Research Centre (JRC), Directorate Health, Consumers and Reference Materials, Chemicals Safety and Alternative Methods Unit, EURL ECVAM, Via E. Fermi 2749, I-21027, Ispra, Varese, Italy

3x *in vitro*

- point mutations in bacteria (AMES)
- chromosome aberrations (numerical and structural) in mammalian cells (*in vitro* MN)
- ~~point mutations (+sometimes structural chromosome aberrations) in mammalian cells (MLA)~~

min. 1x *in vivo*

- ~~point mutations (TGR, *in vivo* Comet)~~
- ~~chromosome aberrations (*in vivo* MN)~~

Recital 40 of Regulation (EC) No 1107/2009: "**Animal testing** for the purposes of this Regulation should be minimised and tests on vertebrates should be undertaken as a last resort."

In vivo test requires demonstration of **target tissue exposure** => how to do this for a natural substance containing many components?

non-testing approaches:

- toxicological threshold of concern (TTC) approach
- (Q)SAR and read-across

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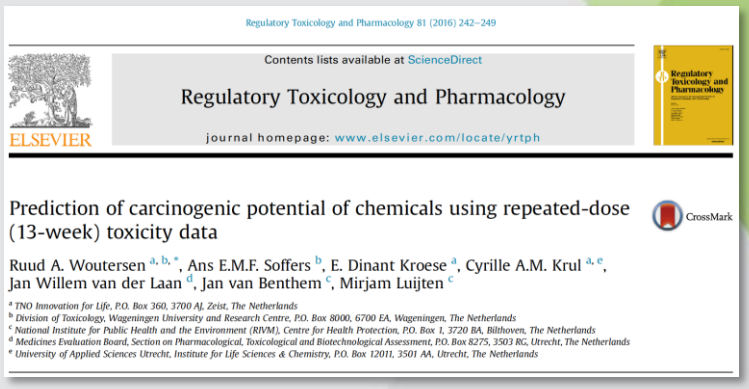
Data requirements for (sub)chronic tox

oral 90-day study in rodent (rat)

oral 90-day study in non-rodent (dog)

- allows to derive a NOAEL
- includes endpoints related to neurotoxicity, immunotoxicity, ED properties
- predictive of carcinogenic potential



Regulatory Toxicology and Pharmacology 81 (2016) 242–249

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Prediction of carcinogenic potential of chemicals using repeated-dose (13-week) toxicity data

Ruud A. Woutersen [a, b, *], Ans E.M.F. Soffers [b], E. Dinant Kroese [a], Cyrille A.M. Krul [a, e], Jan Willem van der Laan [d], Jan van Benthem [c], Mirjam Luijten [c]

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[c] National Institute for Public Health and the Environment (RIVM), Centre for Health Protection, P.O. Box 1, 3720 BA, Bilthoven, The Netherlands
[d] Medicines Evaluation Board, Section on Pharmacological, Toxicological and Biotechnological Assessment, P.O. Box 8275, 3503 RG, Utrecht, The Netherlands
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"chemicals showing no histopathological risk factors for neoplasia in a sub-chronic study in rats may be considered non-carcinogenic and do not require further testing in a carcinogenicity study"

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Data requirements for (sub)chronic tox

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component	% w/w	classification
A	83%	**Acute Tox 4; Skin Corr 1A** (notified)
B	9%	**Eye Dam 1**; Aquatic Chronic 2 (notified)
C	6%	Flam Liq 3; **Acute Tox 3**; **STOT RE1;** Aquatic Acute 1; Aquatic Chronic 3 (harmonised)
D	0.4%	**Skin Sens 1A**; Aquatic Acute 1; Aquatic Chronic 1
Unknown E	0.2%	?
F	0.06%	Skin Sens 1B
G	0.02%	Flam Liq 2; **Skin Sens 1A**

tiered approach, prioritization based on e.g.:
- available information on the components
- presence of components cited in the EFSA compendium

28d study (OECD 407)
90d study (OECD 408,409)


efsa
European Food Safety Authority
EFSA Journal 2012;10(5):2663

SCIENTIFIC REPORT OF EFSA

Compendium of botanicals reported to contain naturally occuring substances of possible concern for human health when used in food and food supplements[1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

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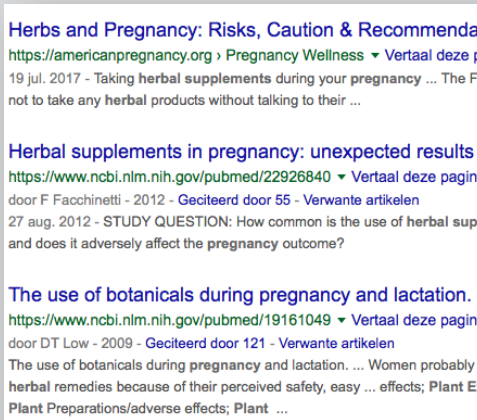
Concern for developmental/reproductive toxicity?

- OECD 421: repr/dev tox screening
- OECD 422: 28d study + repr/dev tox screening
- <-> PNDT/EOGRTS


Herbs and Pregnancy: Risks, Caution & Recommenda
https://americanpregnancy.org › Pregnancy Wellness ▾ Vertaal deze p
19 jul. 2017 - Taking **herbal supplements** during your **pregnancy** ... The F
not to take any **herbal** products without talking to their ...

Herbal supplements in pregnancy: unexpected results
https://www.ncbi.nlm.nih.gov/pubmed/22926840 ▾ Vertaal deze pagin
door F Facchinetti - 2012 - Geciteerd door 55 - Verwante artikelen
27 aug. 2012 - STUDY QUESTION: How common is the use of **herbal sup**
and does it adversely affect the **pregnancy** outcome?

The use of botanicals during pregnancy and lactation.
https://www.ncbi.nlm.nih.gov/pubmed/19161049 ▾ Vertaal deze pagin
door DT Low - 2009 - Geciteerd door 121 - Verwante artikelen
The use of botanicals during **pregnancy** and lactation. ... Women probably
herbal remedies because of their perceived safety, easy ... effects; **Plant E**
Plant Preparations/adverse effects; **Plant** ...

Data requirements for environmental fate

Ready biodegradability test (OECD 301/310)

Careful with interpretation !
- if not readily biodegradable: which component(s)?
- used as food item by the micro-organisms?

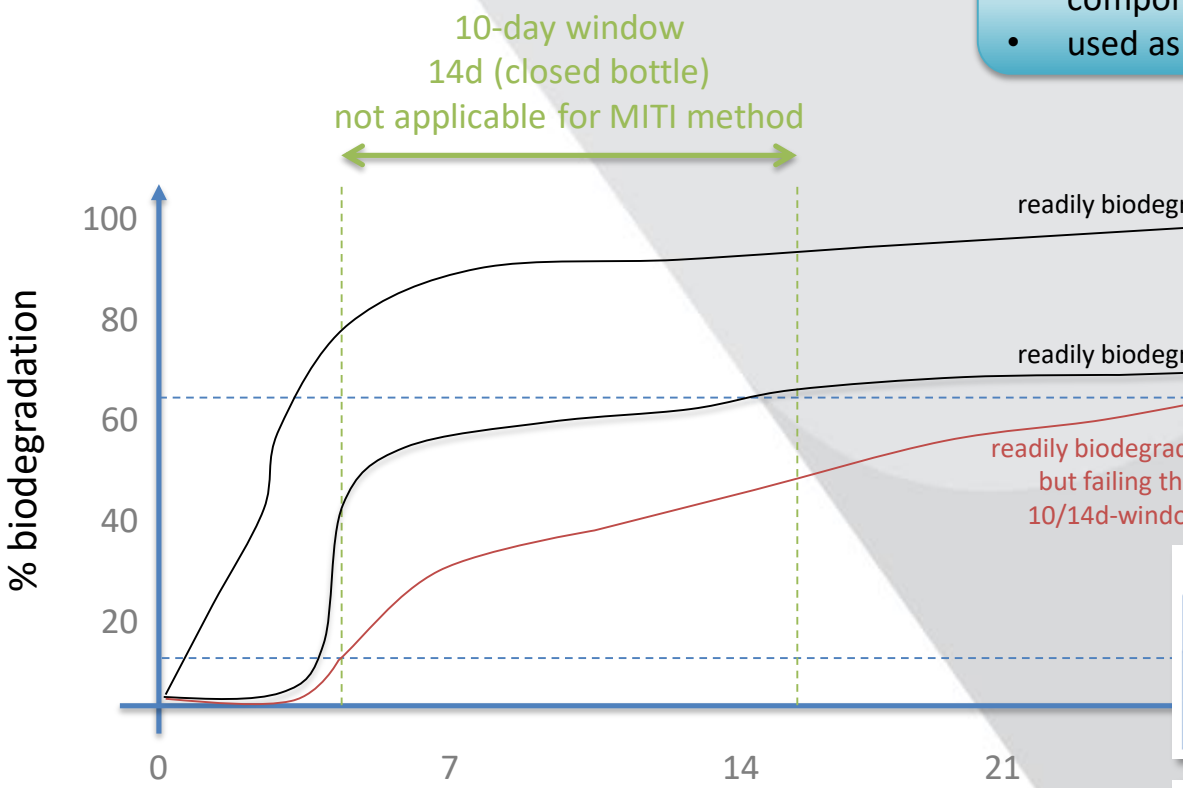


Table R.16-12: Half-lives (days) for (bulk) soil based on results from standardised biodegradation test results

Kp_{soil} [l·kg^{-1}]	Readily biodegradable	Readily biodegradable, failing 10-d window	Inherently biodegradable
≤ 100	30	90	300
>100, ≤ 1 000	300	900	3 000
>1 000, ≤ 10 000	3 000	9 000	30 000
etc.	etc.	etc.	etc.

Table R.16-11: First order rate constants and half-lives for biodegradation i surface water based on results of screening tests on biodegradability[a)]

Test result	Rate constant k (d^{-1})	Half-life (d)
Readily biodegradable	$4.7 \cdot 10^{-2}$	15
Readily, but failing 10-d window [b)]	$1.4 \cdot 10^{-2}$	50
Inherently biodegradable [c)]	$4.7 \cdot 10^{-3}$	150
Not biodegradable	0	∝[43]

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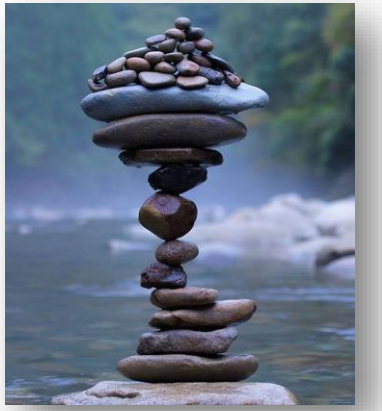
Thank you for your attention



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