

Genotoxicity

In vitro mammalian cell gene
mutation test (OECD 476)

14th May 2013

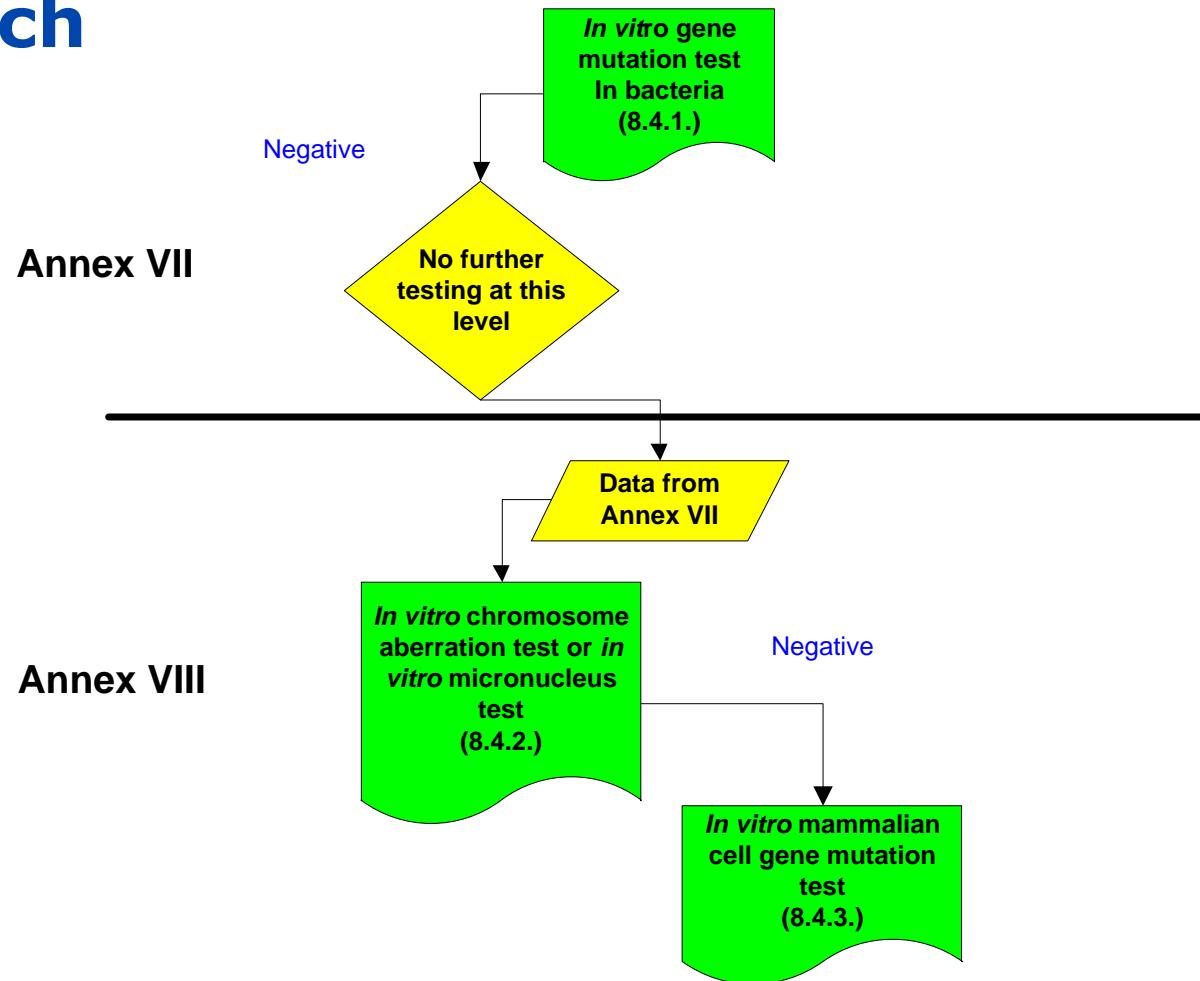
Olli Rahkonen
European Chemicals Agency

Genotoxicity integrated testing strategy

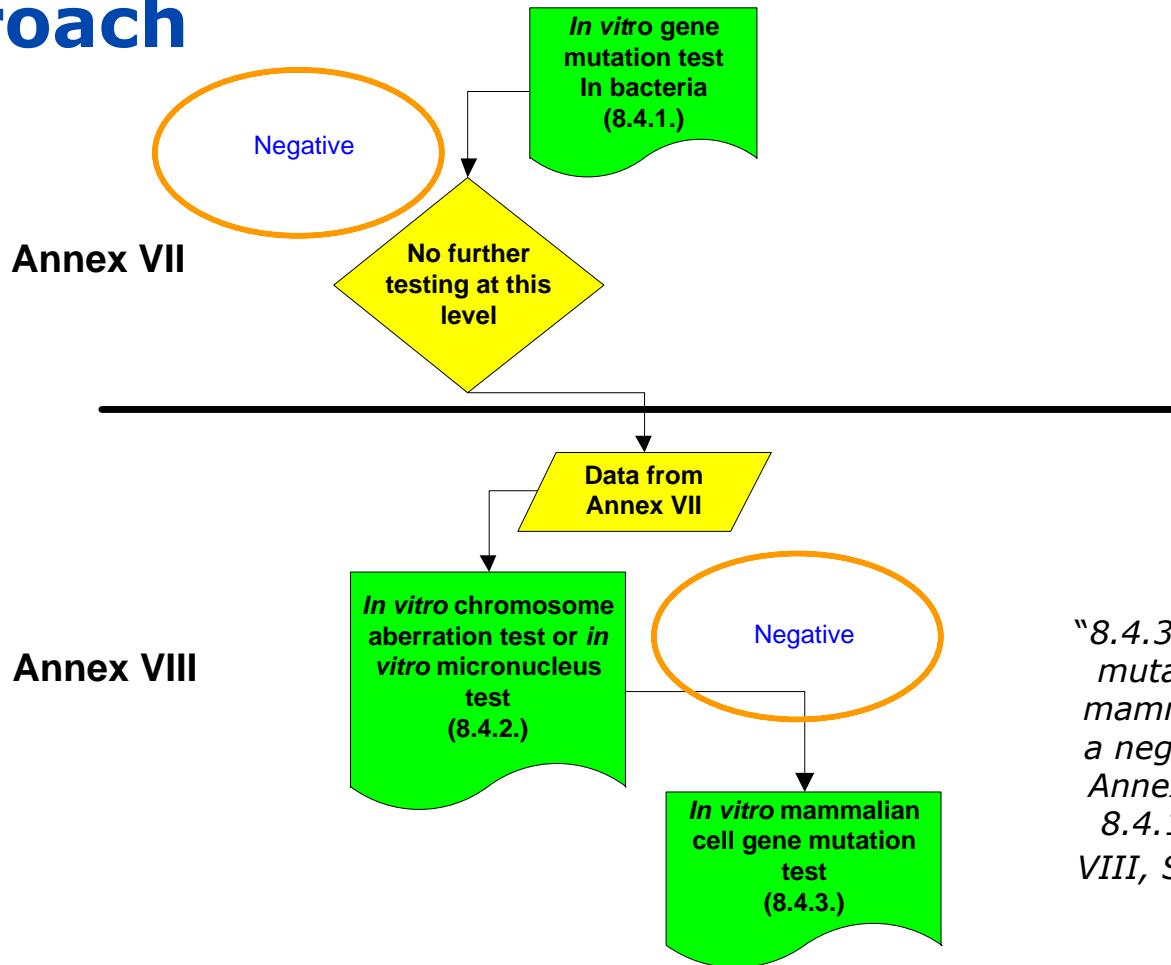
- Genotoxicity integrated testing strategy - webinar available on ECHA webinar's page
- Tips and Hints (part 1) - Genotoxicity

http://echa.europa.eu/view-article/-/journal_content/cda5daf6-7d31-4a07-8d95-c1c820fa802f

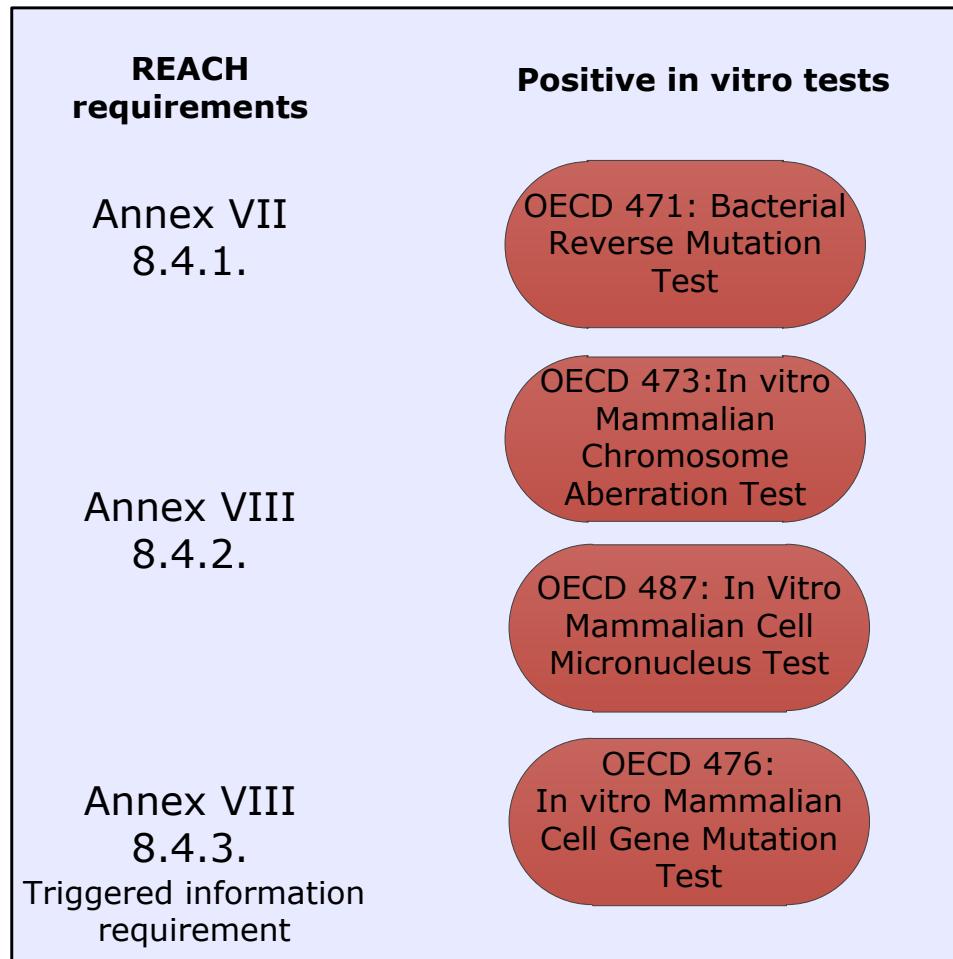
Mutagenicity testing in REACH – a tiered approach



Mutagenicity testing in REACH – a tiered approach



In vivo mutagenicity triggers

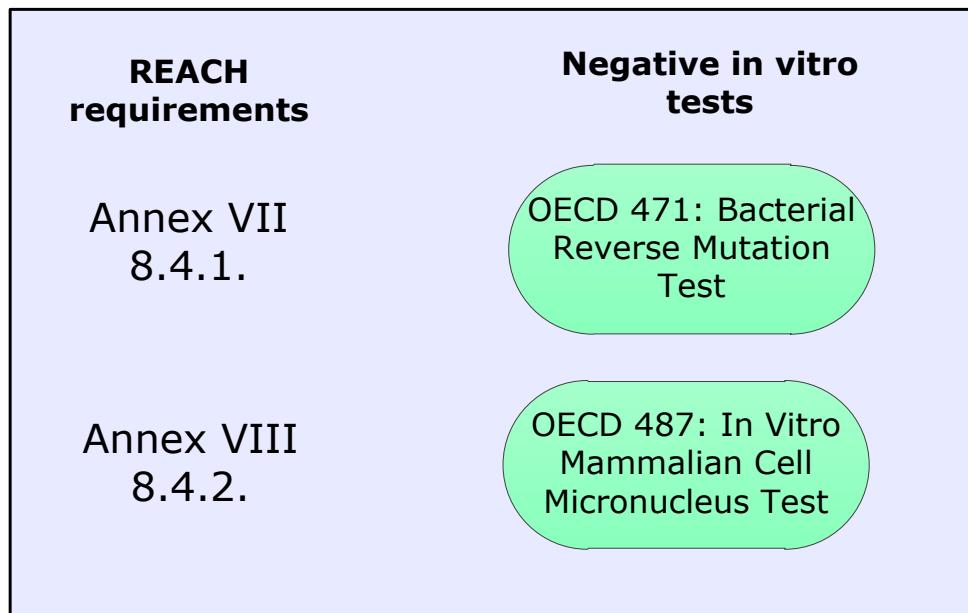


Triggered in vivo tests

"Annex VIII 8.4. Appropriate in vivo mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII."

Triggered *in vitro* mammalian cell gene mutation test

Standard scenario



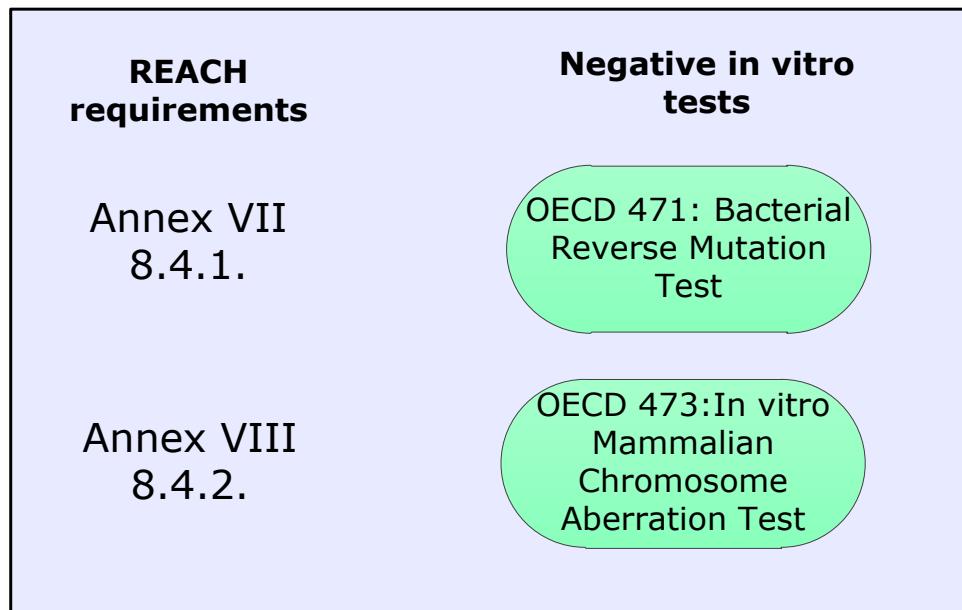
**Annex VIII 8.4.3.
in vitro mammalian cell
gene mutation test
triggered**

OECD 476:
In vitro Mammalian
Cell Gene Mutation
Test

Information gap

Waiving *in vitro* mammalian cell gene mutation test

Column 2 adaptation



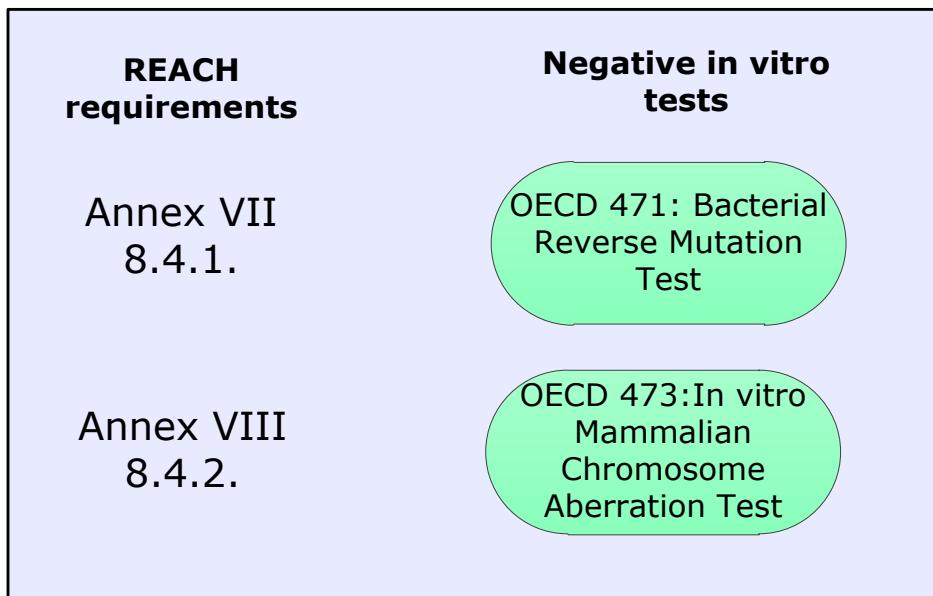
**Annex VIII 8.4.3.
in vitro mammalian cell
gene mutation test
triggered**

8.4.3. column 2
adaptation

*"The study does not usually need to be conducted if adequate data from a reliable *in vivo* mammalian gene mutation test are available."*

Column 2 adaptation

Example 1



- *in vivo* mammalian gene mutation test has not been provided
=> 8.4.3. information gap remains

**Annex VIII 8.4.3.
in vitro mammalian cell
gene mutation test
triggered**

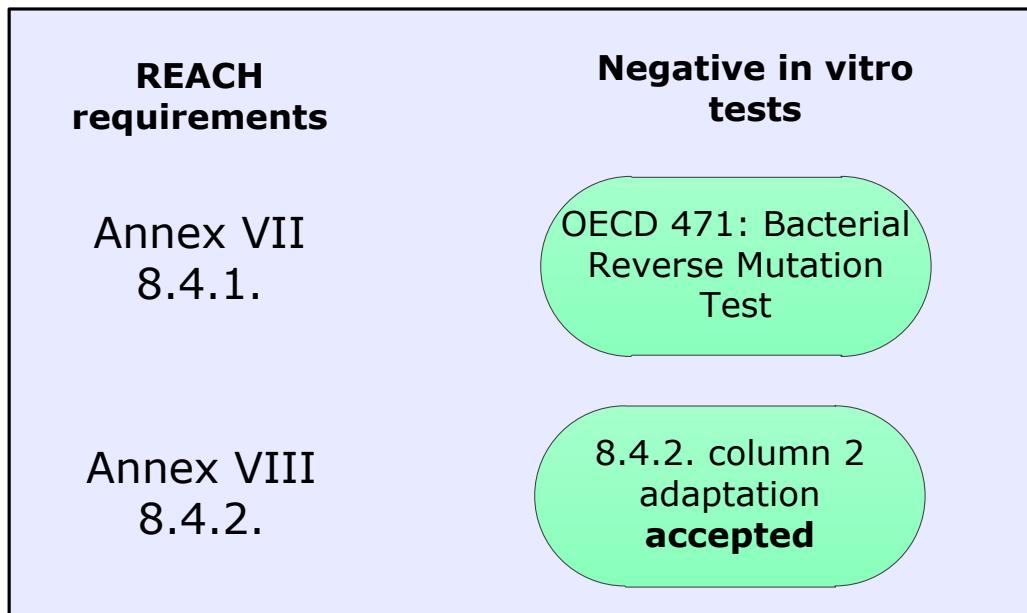
8.4.3. column 2
adaptation

OECD 474:
Mammalian
Erythrocyte
Micronucleus Test

**Adaptation not
accepted**

Multiple column 2 adaptations

Example 2



"The study does not usually need to be conducted — if adequate data from an *in vivo* cytogenicity test are available..."

**Annex VIII 8.4.3.
*in vitro mammalian cell gene mutation test triggered***

8.4.3. column 2 adaptation

**OECD 474:
Mammalian Erythrocyte Micronucleus Test**

Adaptation not accepted for 8.4.3.

Multiple column 2 adaptations

Example 2

REACH requirements	Negative in vitro tests
Annex VII 8.4.1.	OECD 471: Bacterial Reverse Mutation Test
Annex VIII 8.4.2.	8.4.2. column 2 adaptation accepted

*"The study does not usually need to be conducted — if adequate data from an *in vivo* cytogenicity test are available..."*

Annex VIII 8.4.3.
in vitro mammalian cell
gene mutation test
triggered

8.4.3. column 2
adaptation

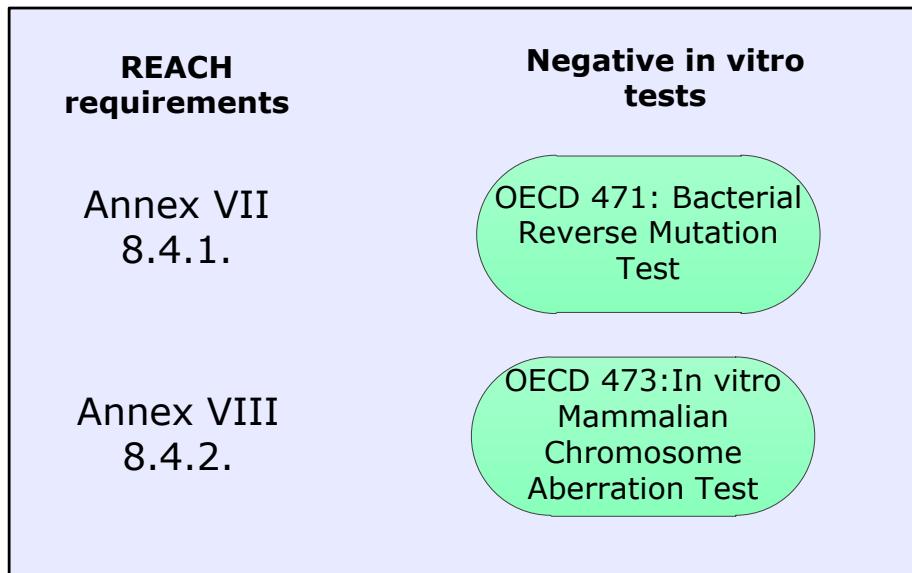
OECD 474:
Mammalian
Erythrocyte
Micronucleus Test

**Adaptation not
accepted for 8.4.3.**

- Waiver is valid on behalf of *in vitro* cytogenicity (8.4.2.) column 2 adaptation
- Waiver not accepted for the *in vivo* mammalian gene mutation test => 8.4.3. information gap remains

Acceptable column 2 adaptation

Example 3



**Annex VIII 8.4.3.
in vitro mammalian cell
gene mutation test
triggered**

**8.4.3. column 2
adaptation**

**OECD 486: UDS
or
OECD 488: TGR**

Adaptation accepted

- *In vivo* gene mutation study provided in the dossier
- => 8.4.3. information gap fulfilled

Read-across

- Study performed on an analogue substance
- Hazard assessment complicated if one or more of the studies are read-across studies

Administrative Data Data source Materials and methods

[Results and discussions](#) [Overall remarks, attachments](#) [Applicant's summary and conclusion](#)

Qualifier	Guideline	
according to	OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test)	no

Principles of method if other than guideline

CLP compliance

yes (incl. certificate)

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

no

Test material identity

Identifier
common name
CAS number

[Add...](#) [Edit...](#) [Delete...](#) [Move up](#) [Move down](#)

Sections

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- [7.4 Sensitisation](#)
- [7.5 Repeated dose toxicity](#)
- [7.6 Genetic toxicity](#)
- [Genetic toxicity](#)
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- [Ames Test;](#)
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- [7.6.2 Genetic toxicity in vivo](#)
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- [7.9 Specific investigations](#)

Read-across

The registrant needs to justify the use of read-across and build the case

- Lead registrant webinar

http://echa.europa.eu/view-article/-/journal_content/e4bf9037-993d-4026-acd7-47e4a7ab62fc

- Experts Workshop on Read-Across Assessment

<http://echa.europa.eu/support/grouping-of-substances-and-read-across>

- ECHA web page support and illustrative examples for grouping of substances and read-across

<http://echa.europa.eu/support/grouping-of-substances-and-read-across>

Thank you