Genotoxicity

In vitro mammalian cell gene mutation test (OECD 476)

14th May 2013

Olli Rahkonen
European Chemicals Agency

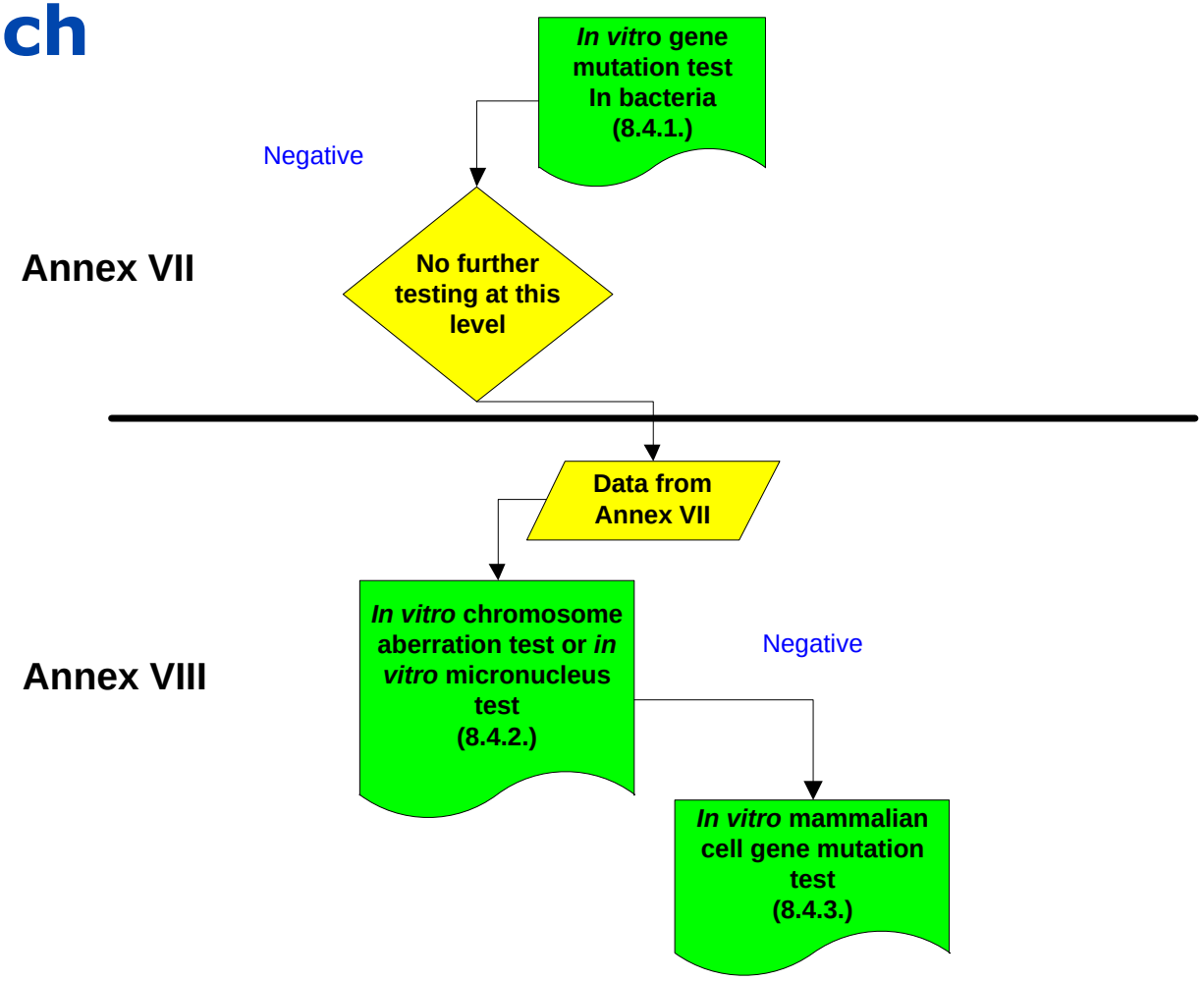
Genotoxicity integrated testing strategy

- Genotoxicity integrated testing strategy - webinar available on ECHA webinar's page

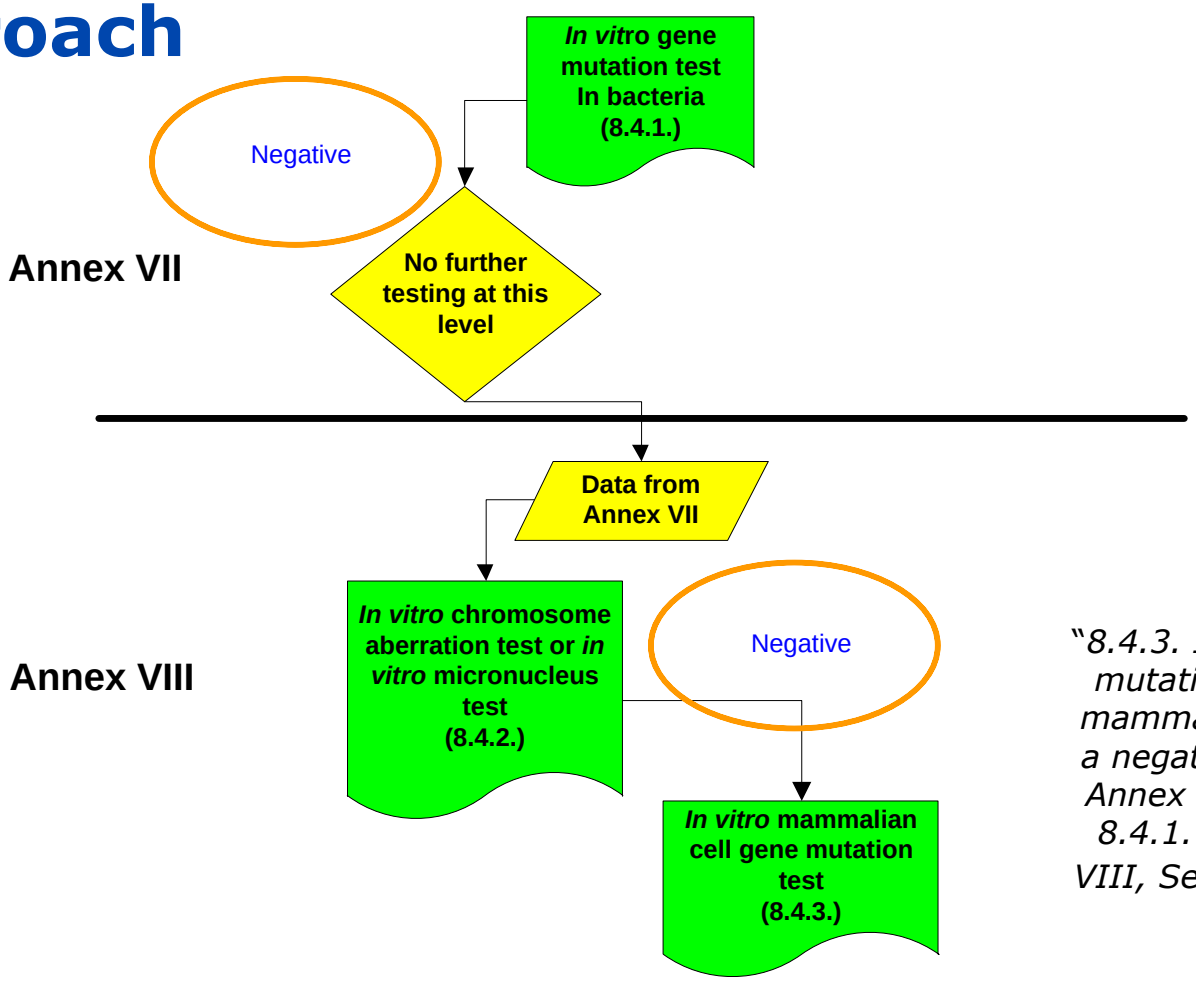
- Tips and Hints (part 1) - Genotoxicity

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

Mutagenicity testing in REACH – a tiered approach

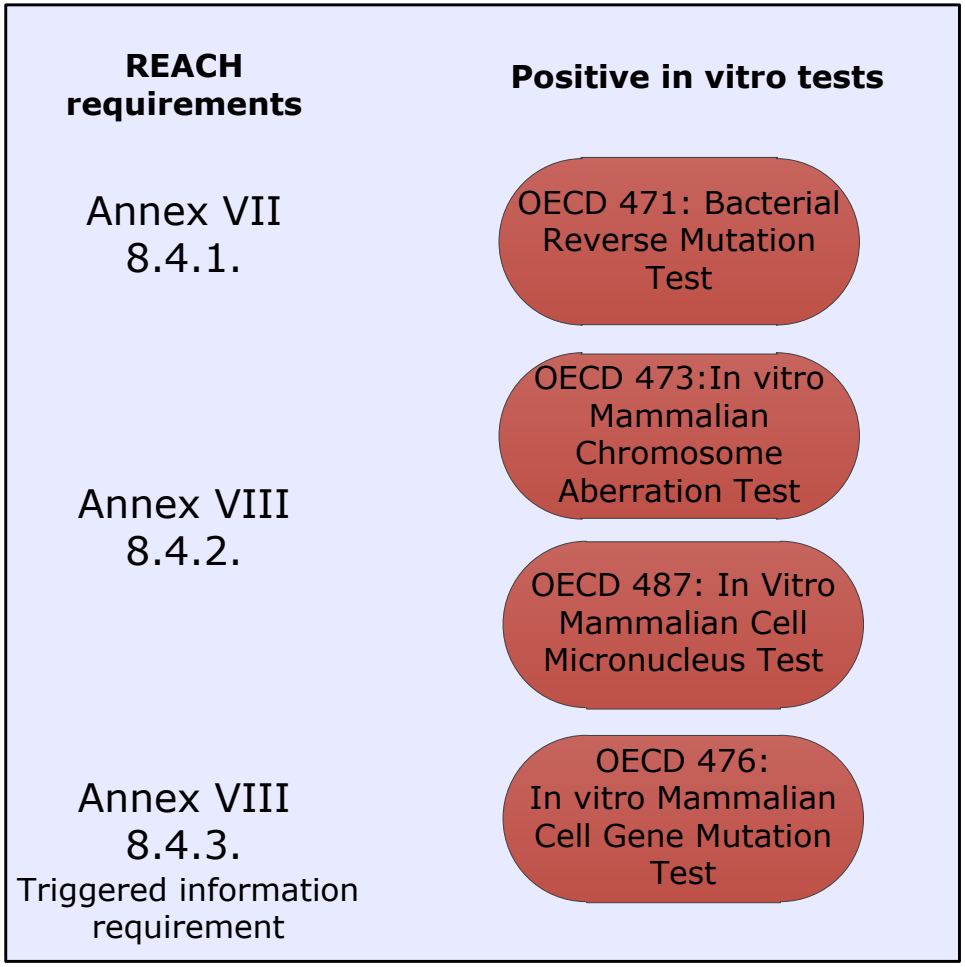


Mutagenicity testing in REACH – a tiered approach



"*8.4.3. In vitro gene mutation study in mammalian cells, if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2.*"

In vivo mutagenicity triggers

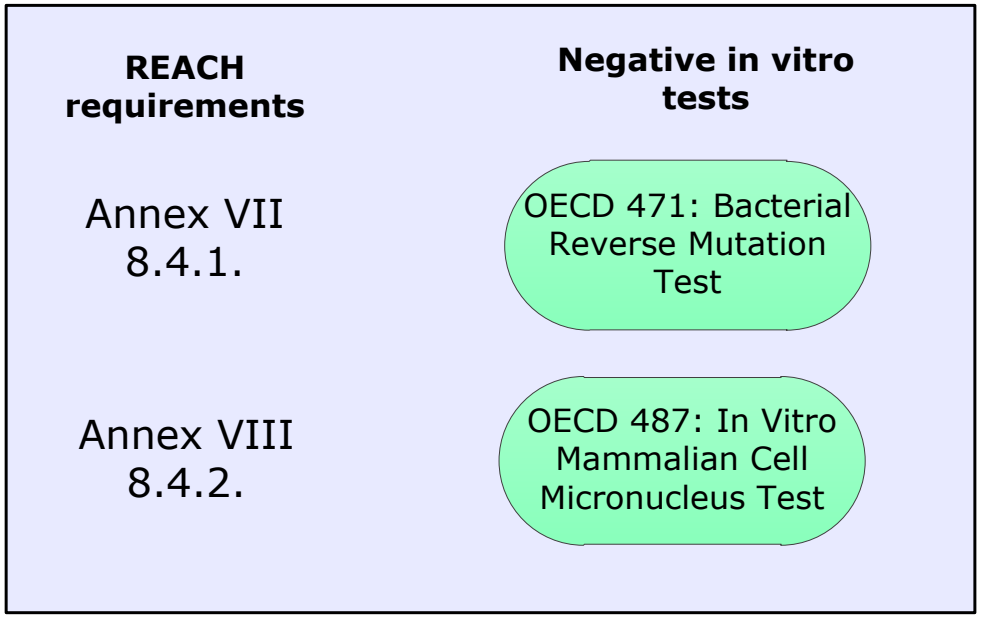


Triggered in vivo tests

"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

REACH requirements	Negative in vitro tests
Annex VII 8.4.1.	OECD 471: Bacterial Reverse Mutation Test
Annex VIII 8.4.2.	OECD 473:In vitro Mammalian Chromosome Aberration Test

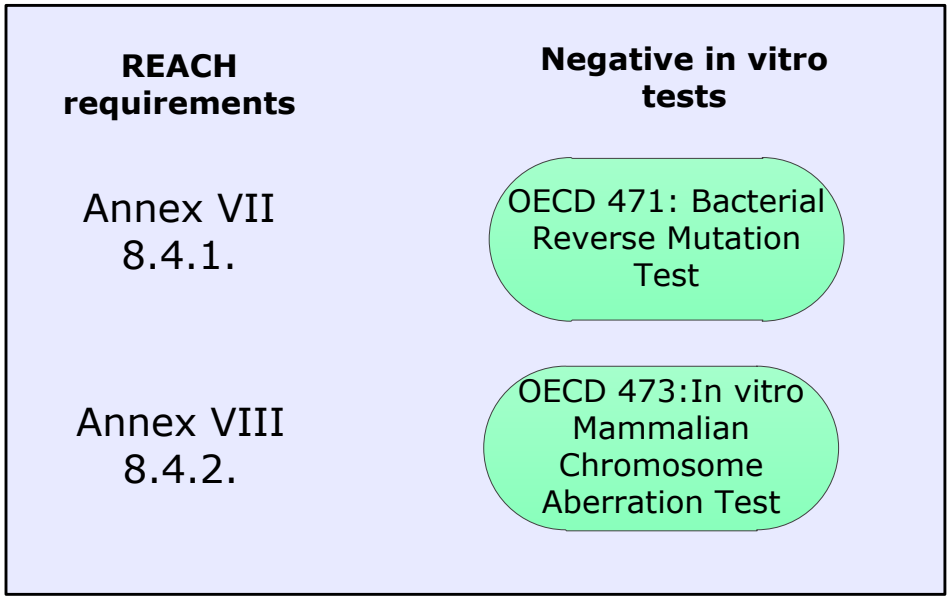
Annex VIII 8.4.3. in vitro mammalian cell gene mutation test triggered

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



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

- *in vivo* mammalian gene mutation test has not been provided

=> 8.4.3. information gap remains

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

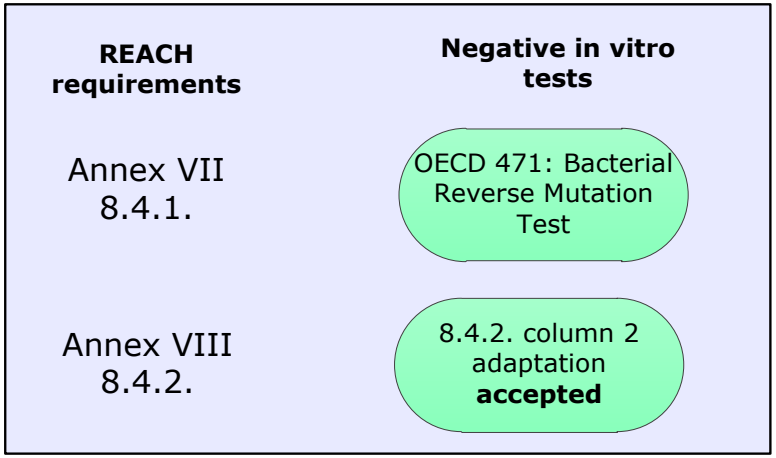
8.4.3. column 2 adaptation

OECD 474: Mammalian Erythrocyte Micronucleus Test

Adaptation not accepted for 8.4.3.

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

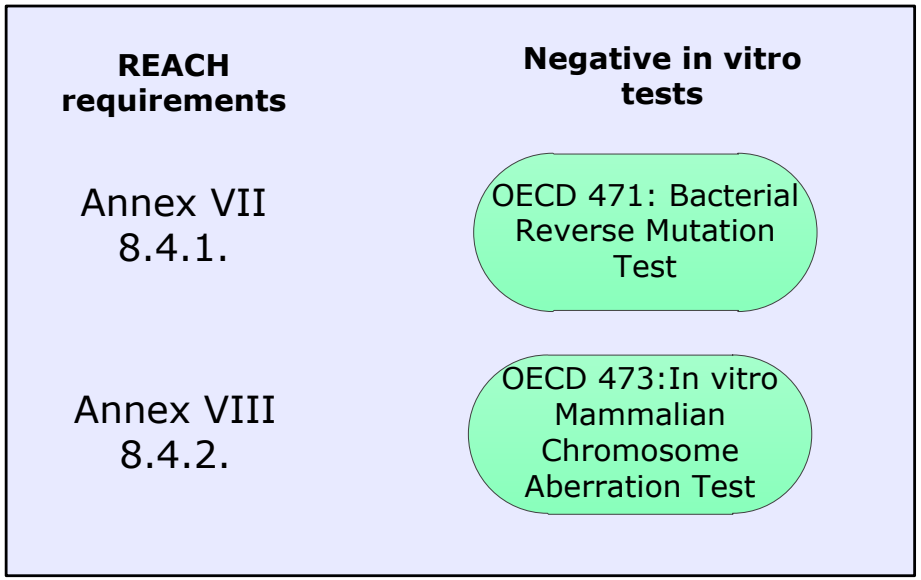
OECD 474: Mammalian Erythrocyte Micronucleus Test

Adaptation not accepted for 8.4.3.

- 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

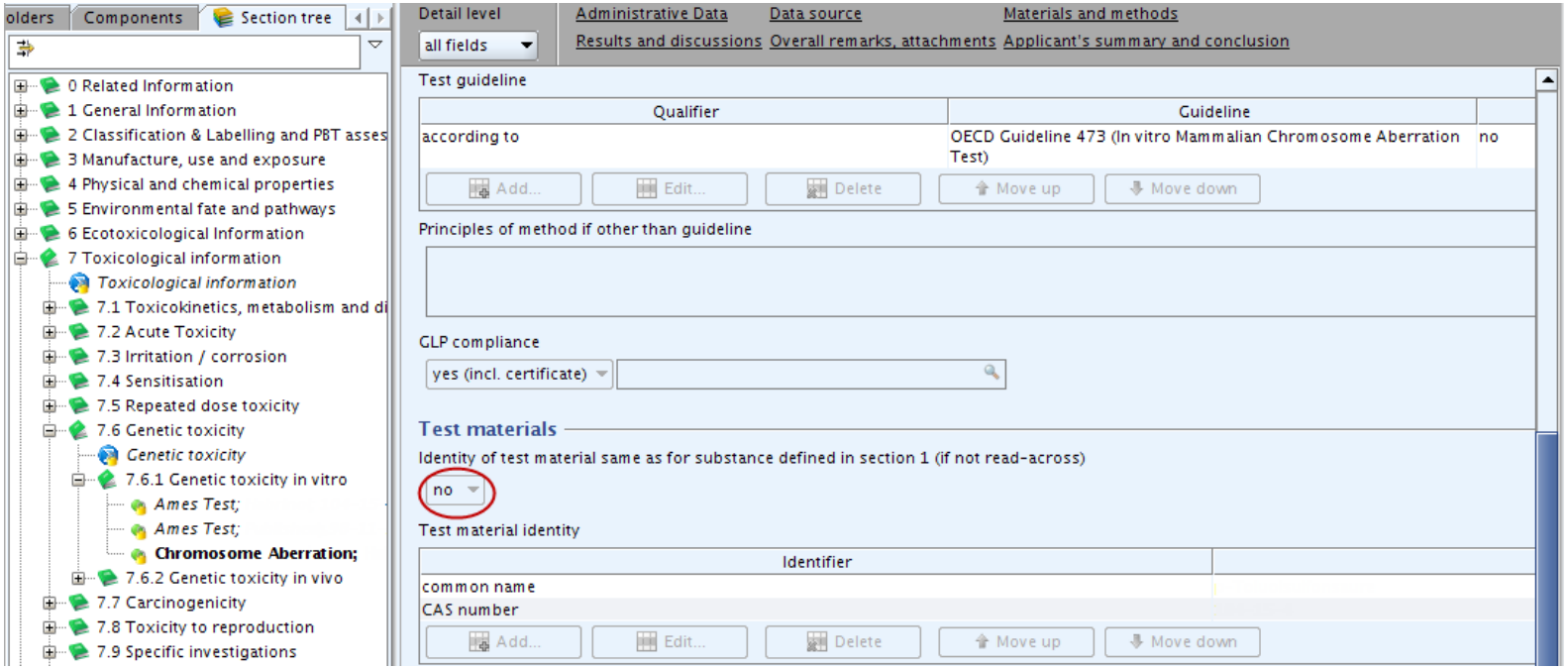
OECD 486: UDS
or
OECD 488: TGR

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



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