

# Results from the Human Health Endpoints

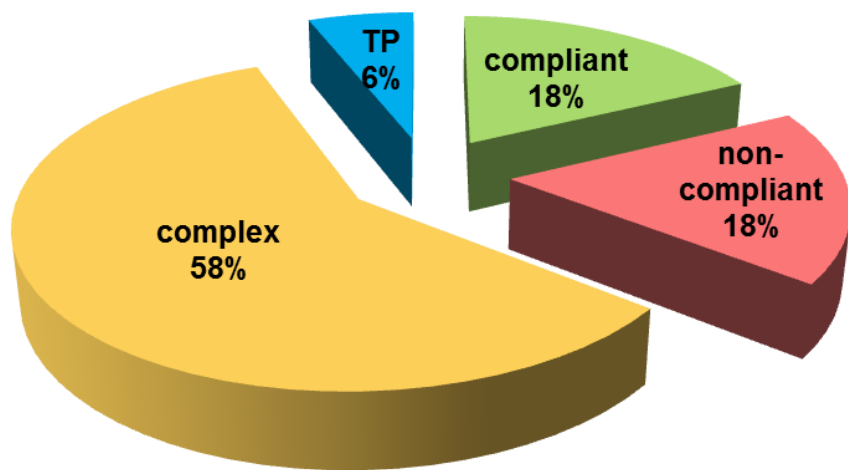
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# Outline

1. Overall Results for Human Health (HH) Endpoints
2. Decisions on the Endpoints - 'Non-compliant' and 'Complex' Cases
  - Repeated Dose Toxicity
  - Toxicity to Reproduction
  - Genetic Toxicity
3. General Reasons for the Decision 'Non-compliant'
4. Adaptations / Waivers in 'Complex' Cases

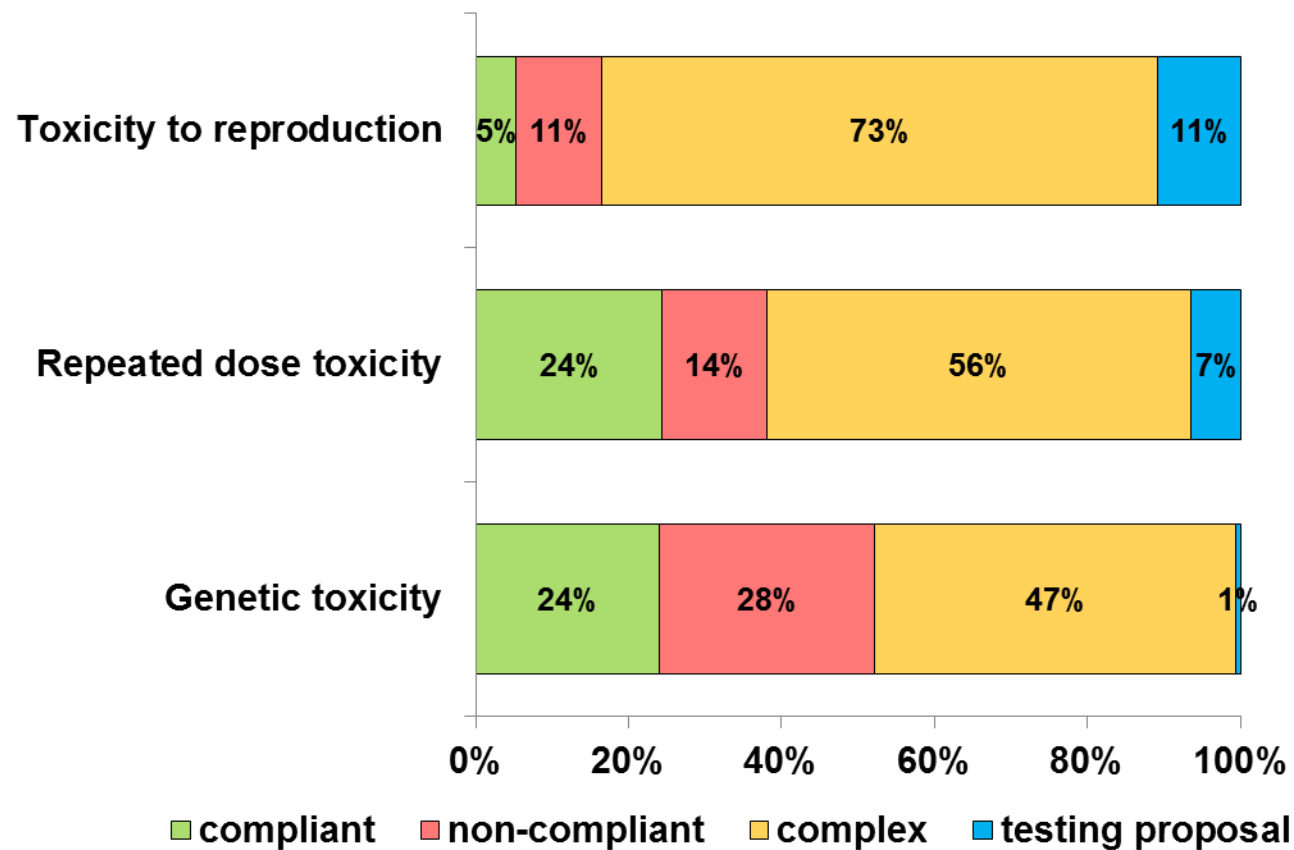
# 1. Overall Results for Human Health Endpoints

**All HH endpoints**



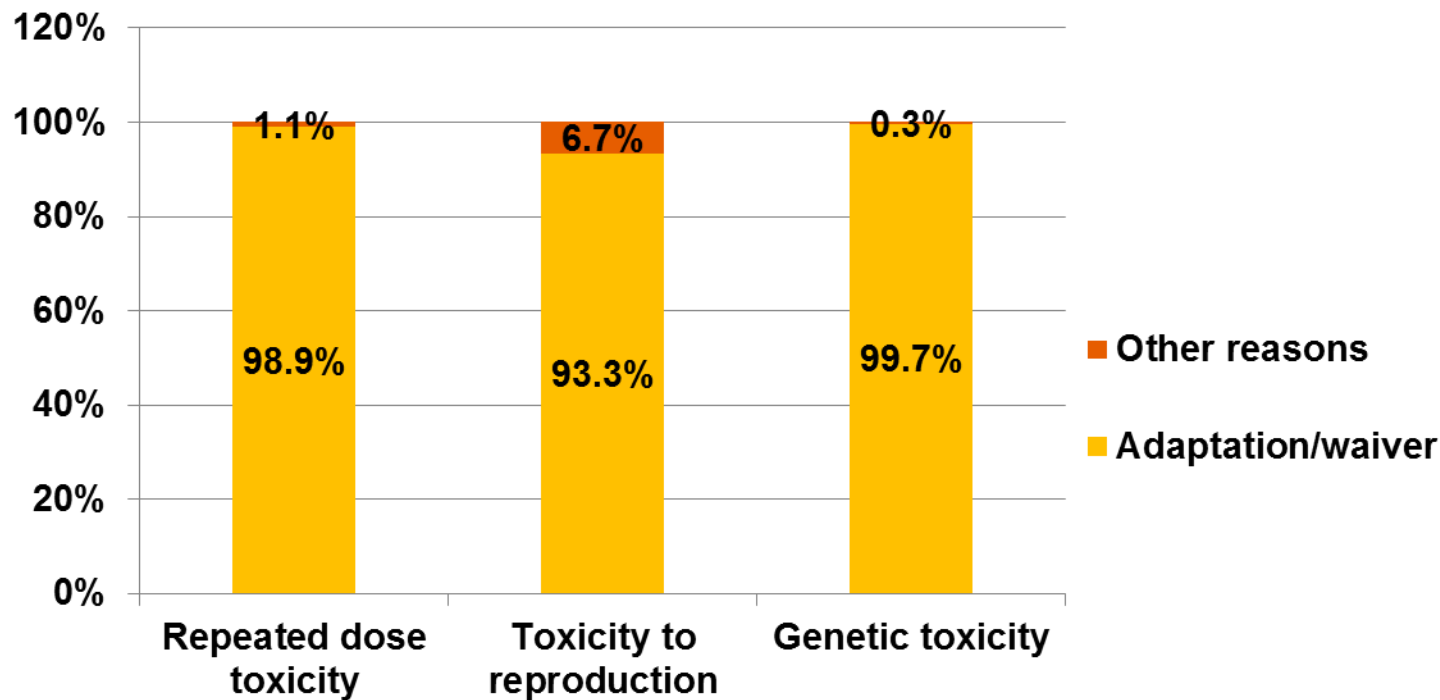
**Accumulated endpoint decisions (5442)**

**Single HH endpoints**



**Single endpoint decisions in 1814 dossiers**

# 1. Overall results: What Includes the Category 'Complex'?



## Meaning of adaptation and waiver (ECHA Practical Guide 4)

- **Adaptation:** Use of non-standard methods for fulfilling information requirements
  - Annex XI 1.1 – 1.5 (Scientific reasons: Use of existing data, Weight of Evidence, (Q)SAR, in vitro methods, grouping/read-across)
- **Waiver:** Submission of standard information is not considered necessary
  - Annex VII to X, Column 2
  - Annex XI, 2 and 3 (Technically, substance-tailored exposure-driven testing)

## 2. Decisions on the Endpoints

- Individual decision 'profile' for each endpoint
- What endpoint- specific reasons caused the decisions?

**'non-compliant'**

Non-compliant to REACH Annexes VII-X

**'complex'**

Not (yet) decided due to waiving or adaptation according to REACH Annexes VII-X, Column 2 or Annex XI or other reasons not assessable due to time limitations

**'testing proposal'**

No further endpoint screening

**'compliant'**

Compliant to REACH Annexes VII-X including Column 2 criteria regarding a harmonised classification

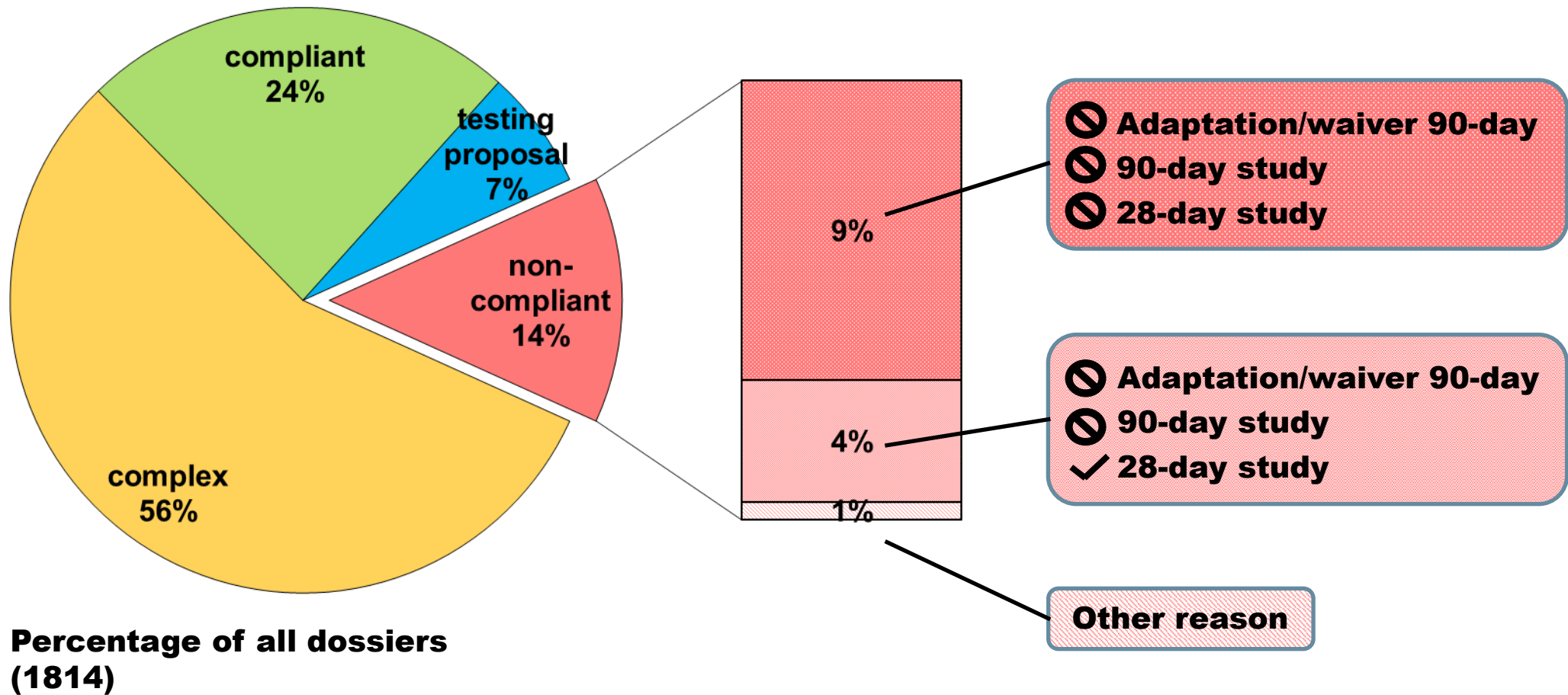
## 2. Repeated Dose Toxicity – REACH Standard Information Requirements

Production volume  $\geq$  1000 t/a

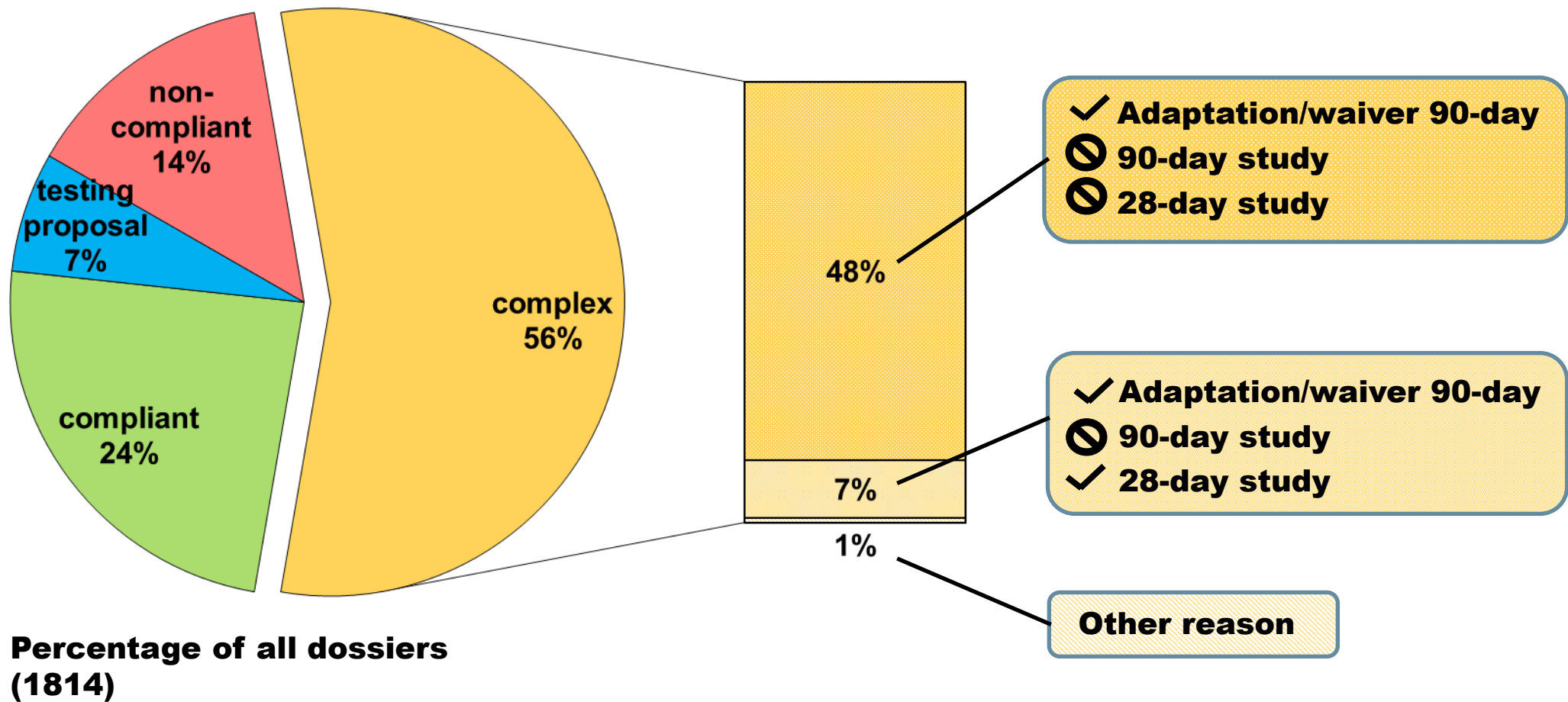
- 90-day study
- 28-day study (not required if 90-day study available)

Alternative: Adaptations / waiving according to Annex VIII to X, Column 2 or Annex XI

## 2. Repeated Dose Toxicity – Decision ‘Non-compliant’



## 2. Repeated Dose Toxicity – Decision ‘Complex’





## 2. Repeated Dose Toxicity – Single Case Analysis of ‘Complex’ Cases

**12 analysed** → **7 ‘non-compliant’**  
 → **5 ‘complex’**

Revised decision	Reason
<b>Non-compliant</b>	Waiving insufficient with respect to conditions stated in one <ul style="list-style-type: none"> <li>• Annex IX, 8.6.2., Column 2</li> <li>• Annex X, paragraph 4 (corrosive substance)</li> <li>• Annex X, paragraph 5 (data waiving due to other reasons)</li> </ul>
<b>Non-compliant</b>	No waiver for standard information requirements, waiver exists only for non-required studies
<b>Complex</b>	More detailed analysis required with respect to: <ul style="list-style-type: none"> <li>• Annex XI (1.2. weight of evidence; 3. exposure considerations)</li> <li>• Annex IX, 8.6.2., Column 2</li> </ul>

**28-day study shows no or low toxicity, additional properties not considered**

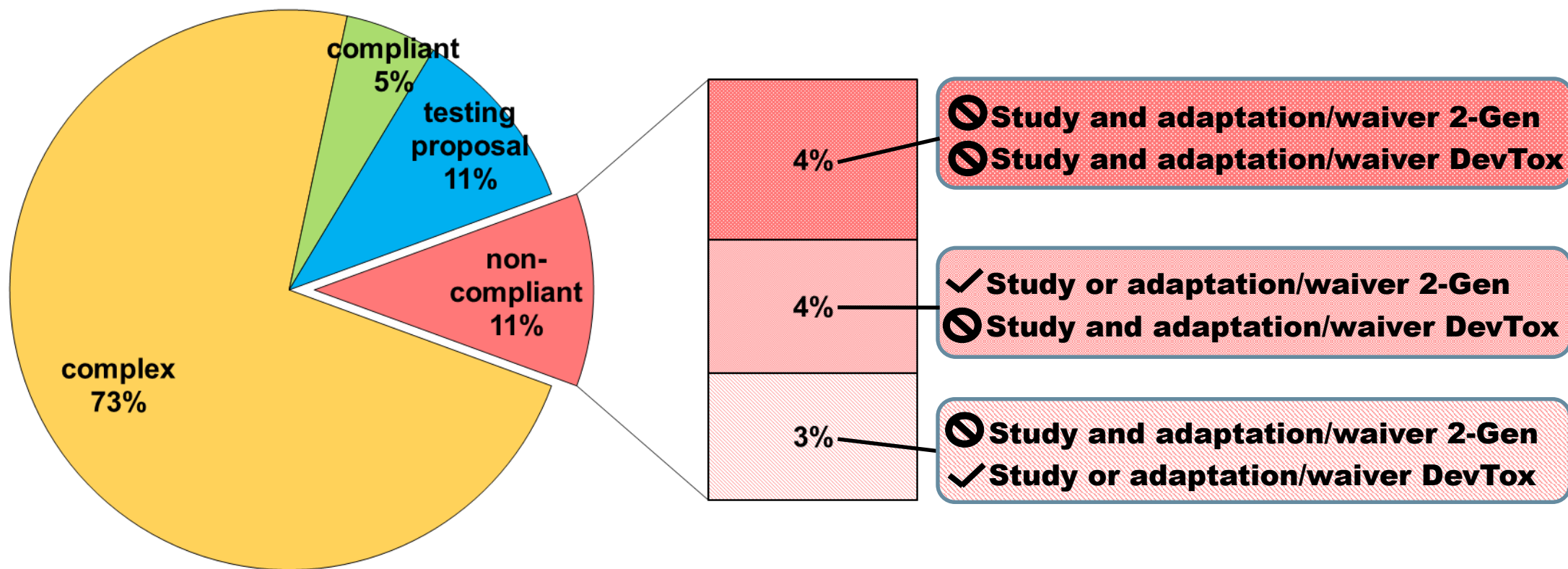
### 3. Toxicity to Reproduction – REACH Standard Information Requirements

Production volume  $\geq$  1000 t/a

- Prenatal developmental toxicity study (one or two species) (DevTox)
- Two-generation study (2-Gen)

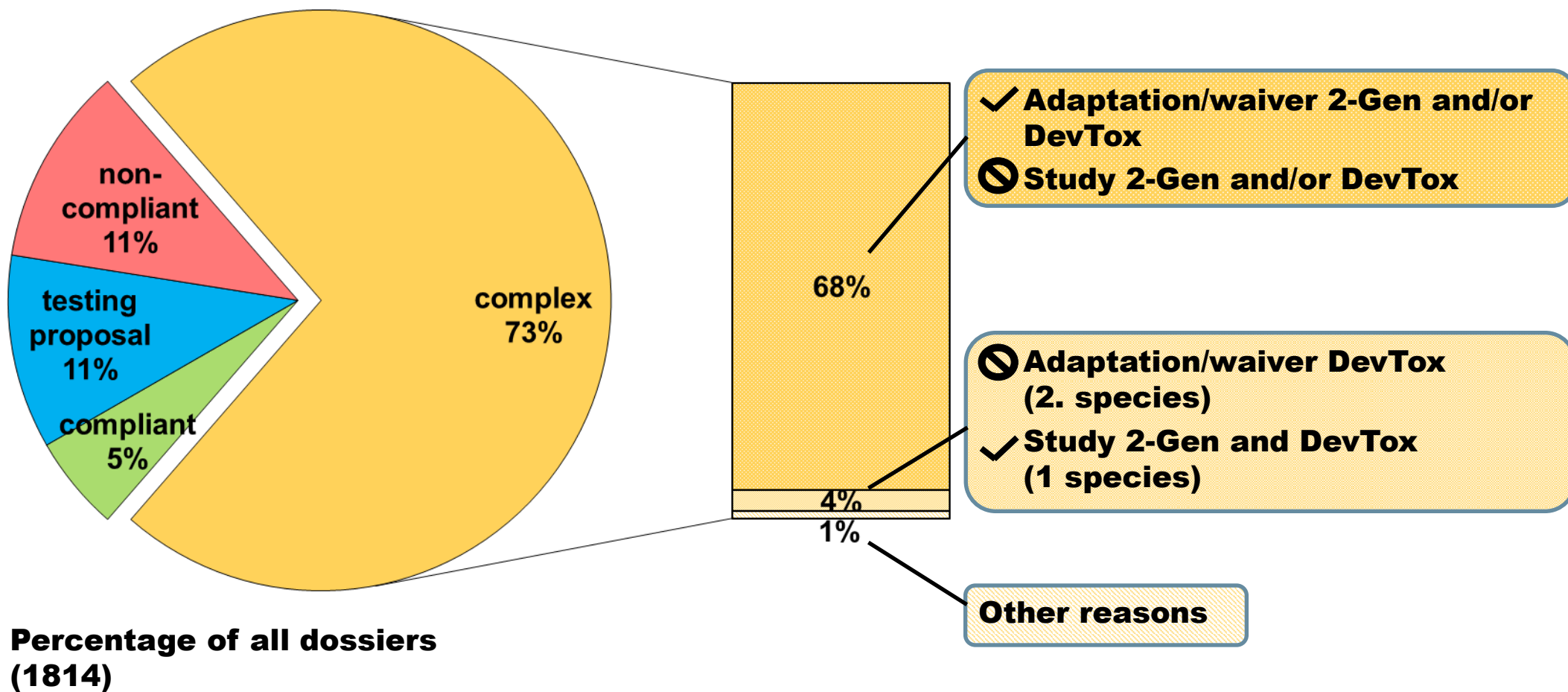
Alternative: Adaptations / waiving according to Annex VIII to X, Column 2 or Annex XI

### 3. Toxicity to Reproduction – Decision ‘Non-compliant’



**Percentage of all dossiers (1814)**

### 3. Toxicity to Reproduction – Decision ‘Complex’

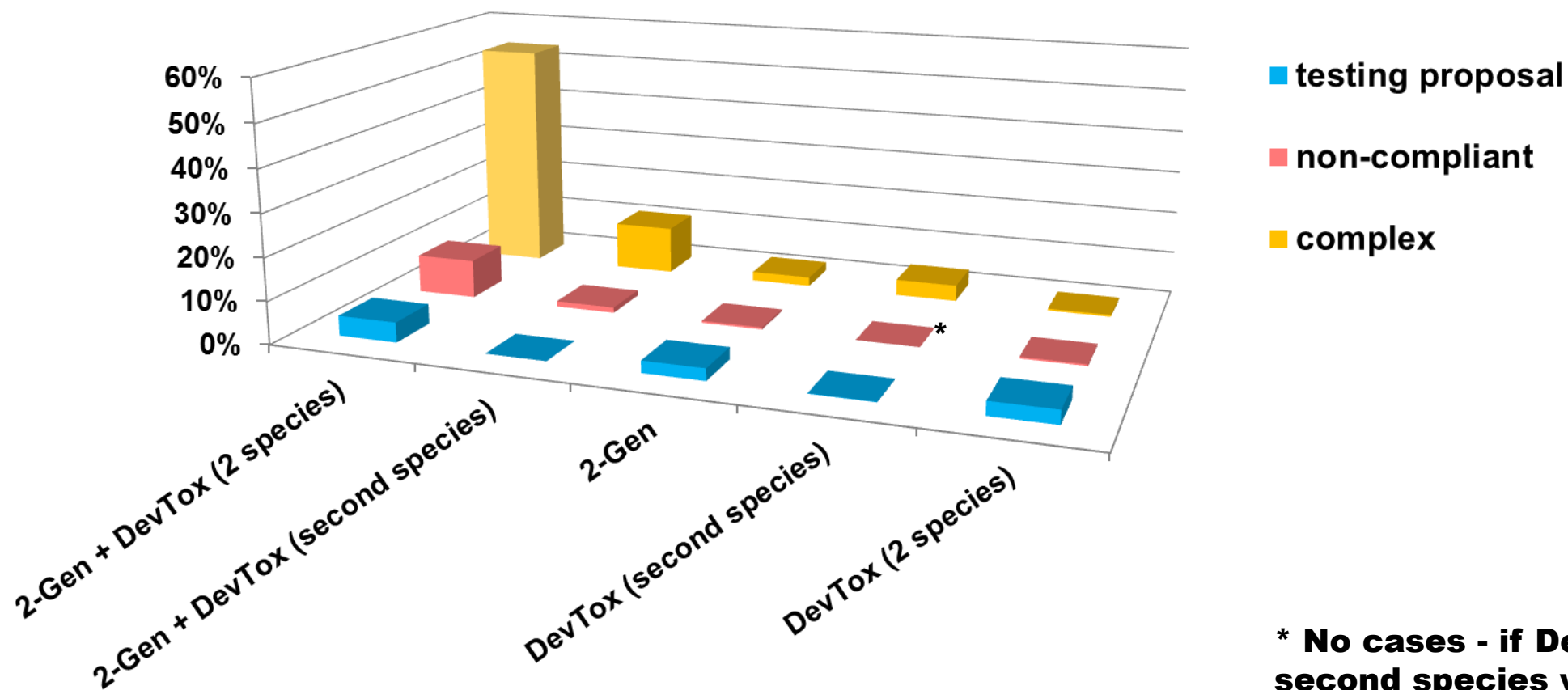


### 3. Toxicity to Reproduction – Standard Information not available

2-Gen study: ~85% of all dossiers

DevTox (2 species): ~70% of all dossiers

DevTox (second species): ~90% of all dossiers



**Missing study types (% of all dossiers)**

**\* No cases - if DevTox in second species was missing the cases were assigned to 'complex'**

### 3. Toxicity to Reproduction – Single Case Analysis of ‘Complex’ Cases

**26 analysed** → **23 ‘non-compliant’**  
 → **3 ‘compliant’**

**Administration route appropriate**

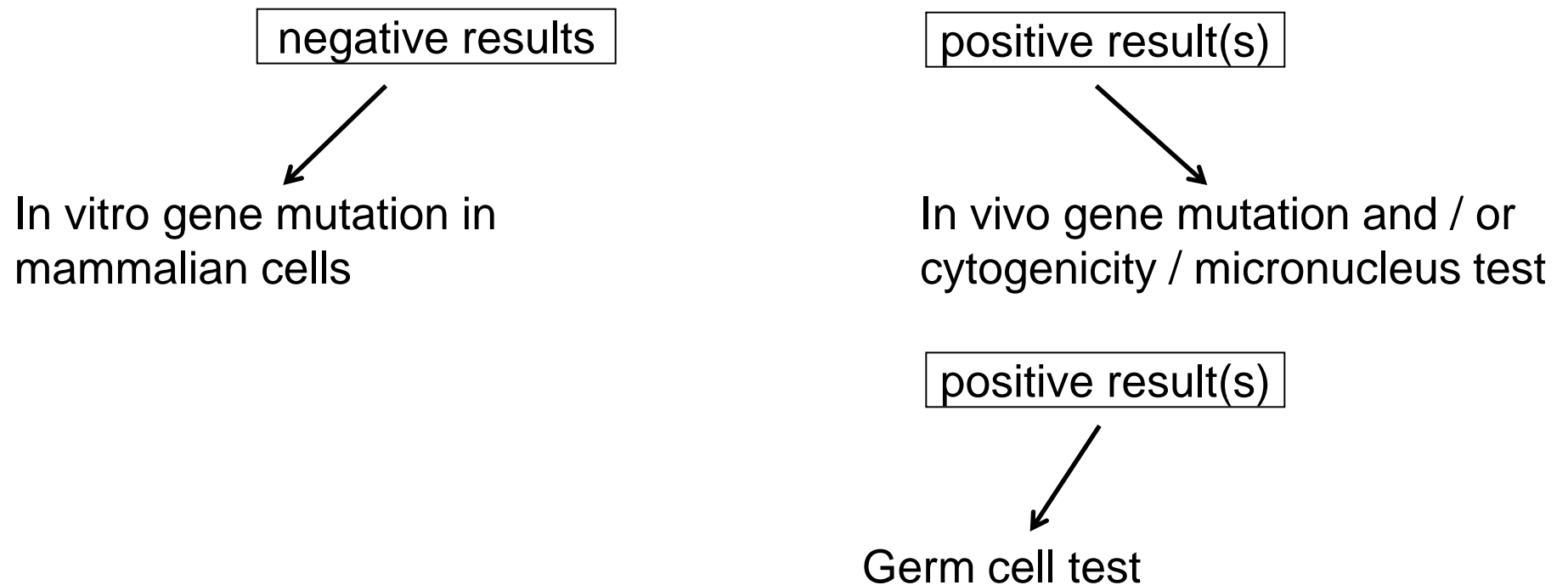
Revised decision	Reason
Compliant	Most relevant administration route was chosen
Compliant	Waiving sufficient with respect to: <ul style="list-style-type: none"> <li>Annex X, 8.7., Column 2</li> </ul>
Compliant	Substance is classified according to CLP as muta. cat. 1
Non-compliant	Adaptation / waiver insufficient with respect to conditions <ul style="list-style-type: none"> <li>Annex X, 8.7., Column 2</li> <li>Annex X, paragraph 4 (corrosive substance)</li> <li>Annex X, paragraph 5 (data waiving due to other studies)</li> <li>Annex XI (1.1. use of existing data; 1.2. weight of evidence)</li> <li>Reference to another, inappropriate Annex</li> </ul>
Non-compliant	Study and adaptation/waiver for TG 414, second species, is not available
Non-compliant	Substance-related issues: <ul style="list-style-type: none"> <li>Test was not conducted with registered substance</li> <li>Composition of the registered chemical is not sufficiently specified, but required for evaluation</li> </ul>
Non-compliant	No waiver for standard information requirements, waiver exists only for non-required studies
Non-compliant	Required information is not available <ul style="list-style-type: none"> <li>Required studies are incomplete (Annex X, 8.7.2.), Column 1</li> <li>Required studies are not available (Annex X, 8.7.2., Column 1; Annex XI, 1.5 grouping/read-across)</li> </ul>

**Other studies show no or low toxicity, additional properties not considered**

## 4. Genetic Toxicity – REACH Standard Information Requirements

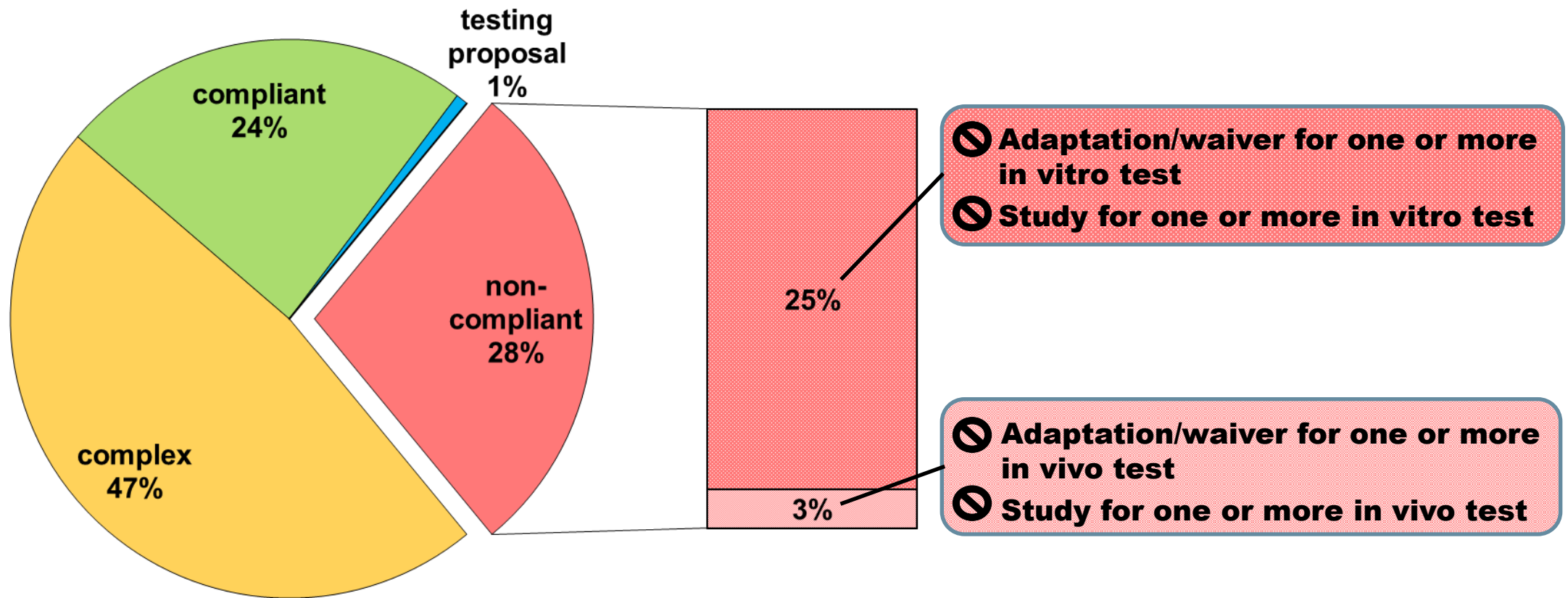
Production volume  $\geq$  1000 t/a

- In vitro gene mutation in bacteria
- In vitro cytogenicity / micronucleus test in mammalian cells



Alternatives: Adaptations / waiving according to Annex VIII to X, Column 2 or Annex XI

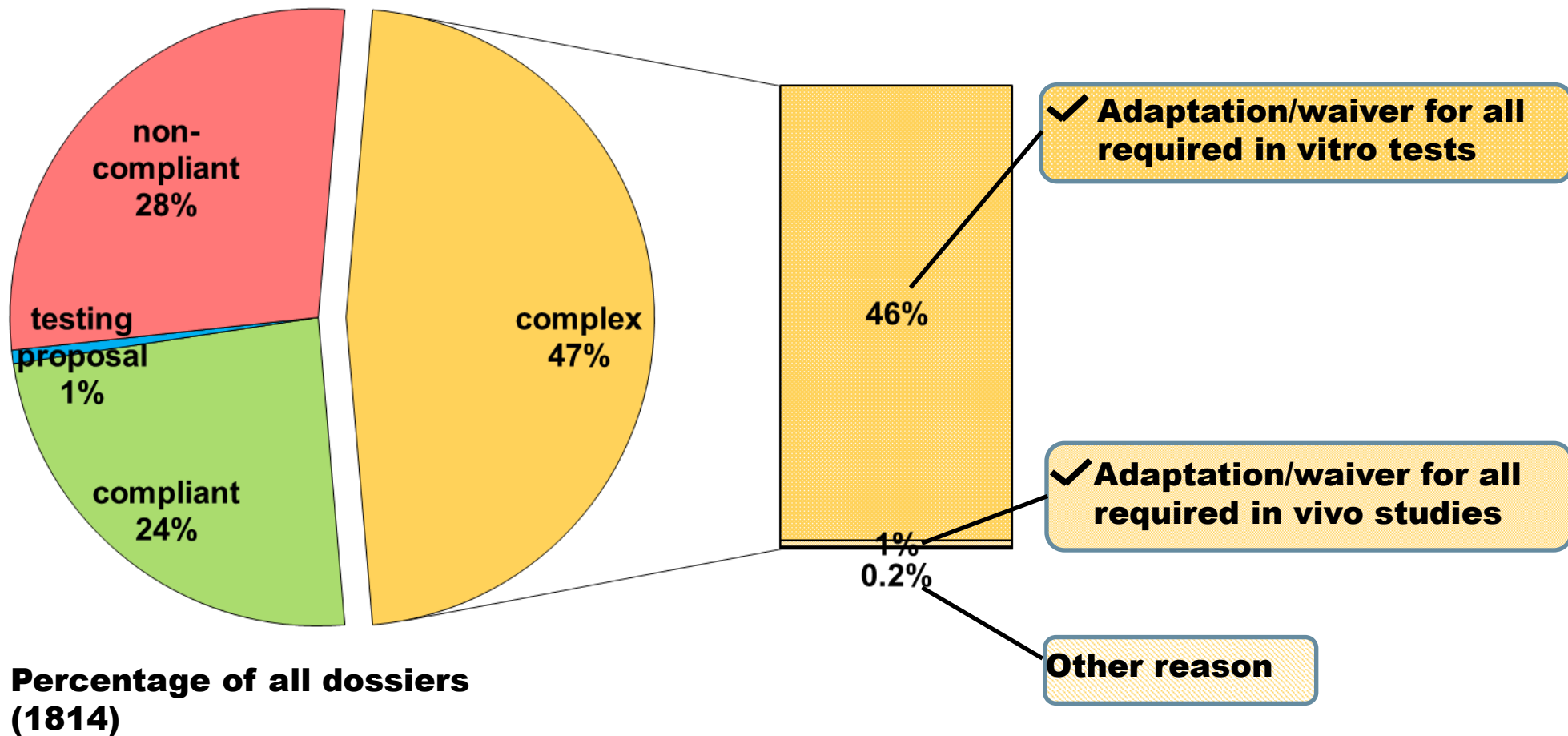
## 4. Genetic Toxicity – Decision ‘Non-compliant’



**Percentage of all dossiers  
(1814)**

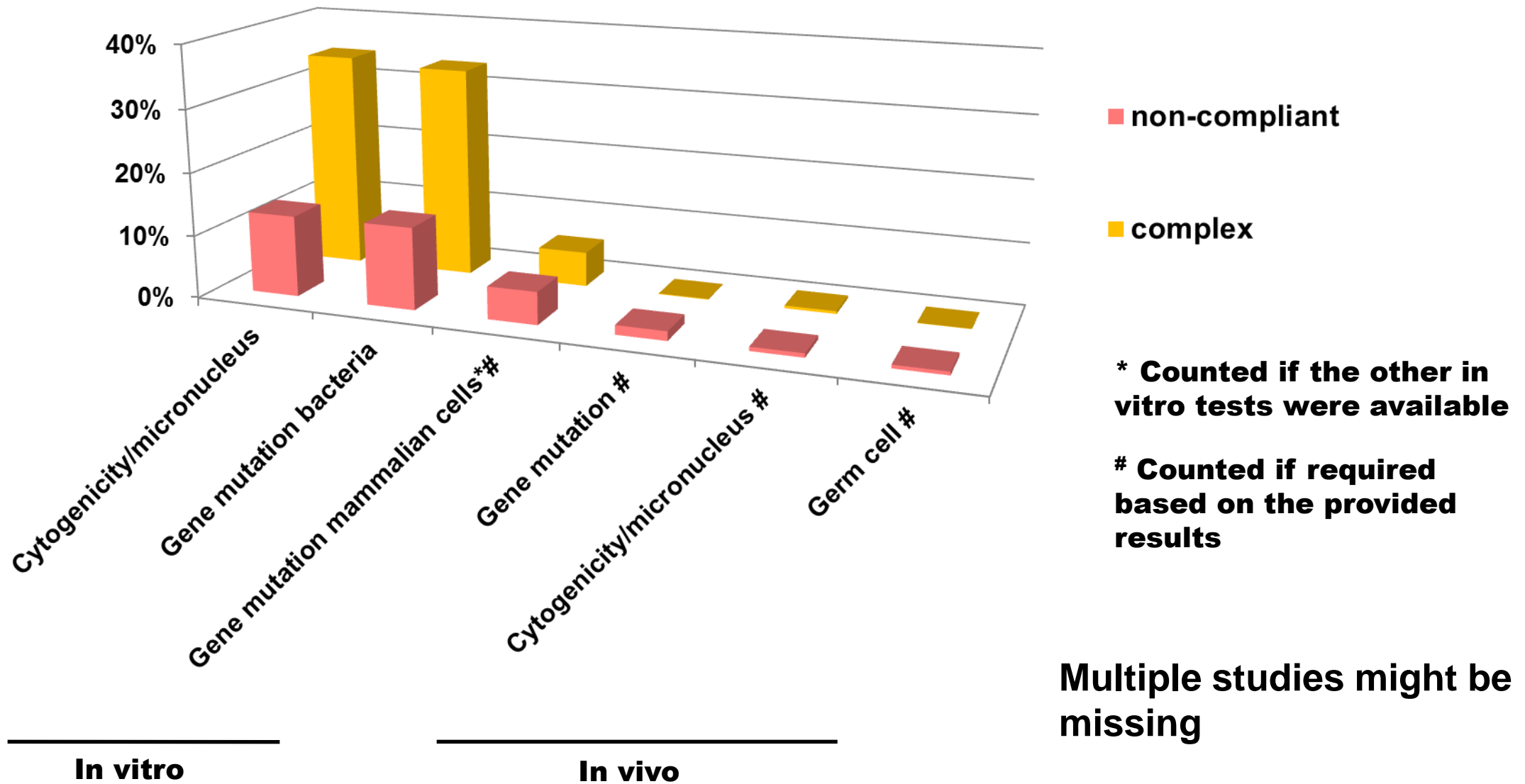


## 4. Genetic Toxicity – Decision ‘Complex’

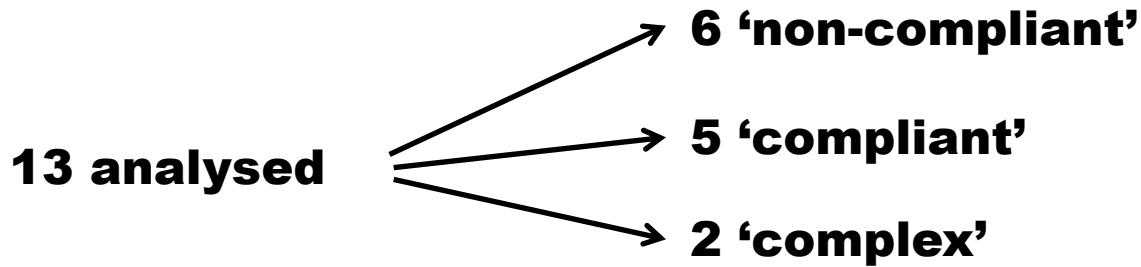


# 4. Genetic Toxicity – Standard Information not available

## Missing study types (% of all dossiers)



# 4. Genetic Toxicity – Single Case Analysis of ‘Complex’ Cases



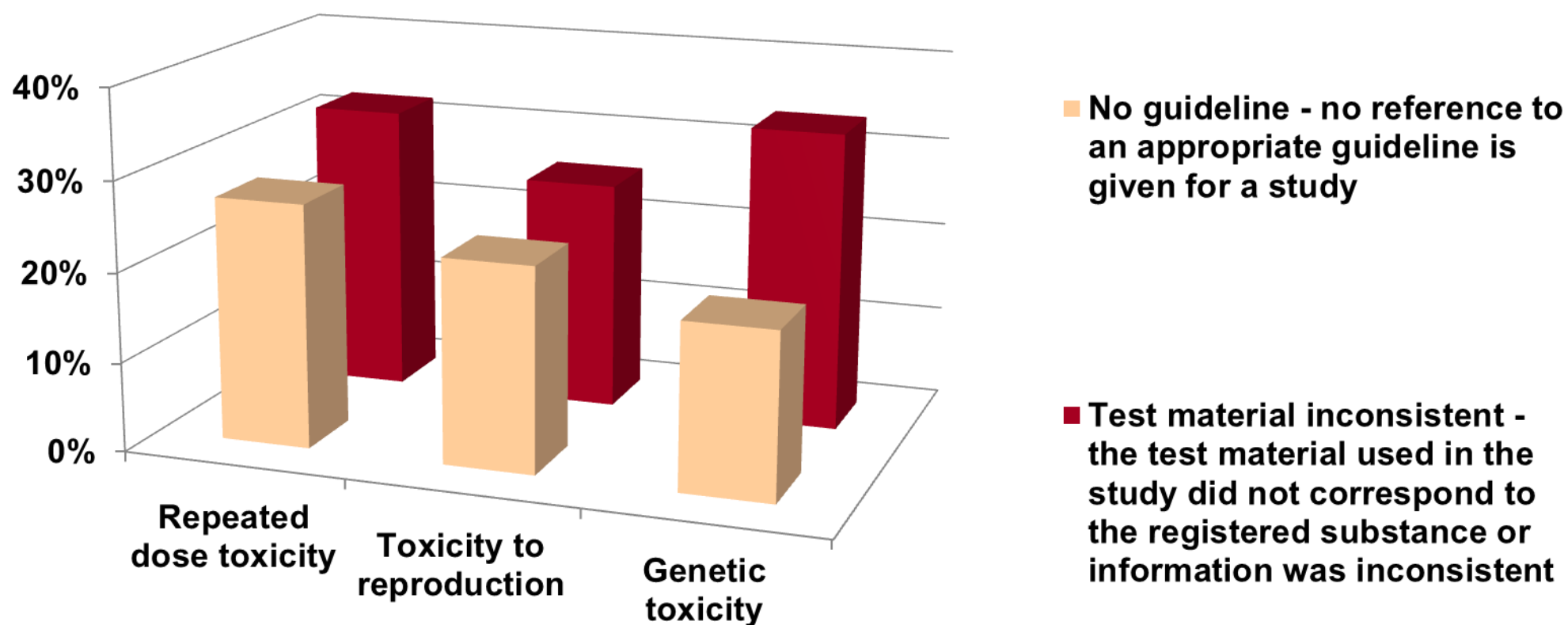
**All components are listed in Annex IV**

Revised decision	Reason
Compliant	Waiving sufficient with respect to conditions stated in one of the following Annexes: <ul style="list-style-type: none"> <li>• Annex X, paragraph 5 (data waiving due to other reasons)</li> <li>• Annex IV</li> </ul>
Compliant	Substance is classified according to CLP as muta. cat. 1 or carc. cat. 1
Non-compliant	Adaptation insufficient with respect to: <ul style="list-style-type: none"> <li>• Annex XI (1.2. weight of evidence)</li> </ul>
Non-compliant	Required information is not available <ul style="list-style-type: none"> <li>• Required studies are incomplete (Annex VII, 8.4.1., Column 1)</li> <li>• Required studies are not available (Annex VIII, 8.4.3., Column 1; Annex IX, 8.4., Column 2)</li> </ul>
Complex	More detailed analysis required with respect to: <ul style="list-style-type: none"> <li>• Annex XI</li> </ul>

**Data for the 5th bacterial strain were not provided**

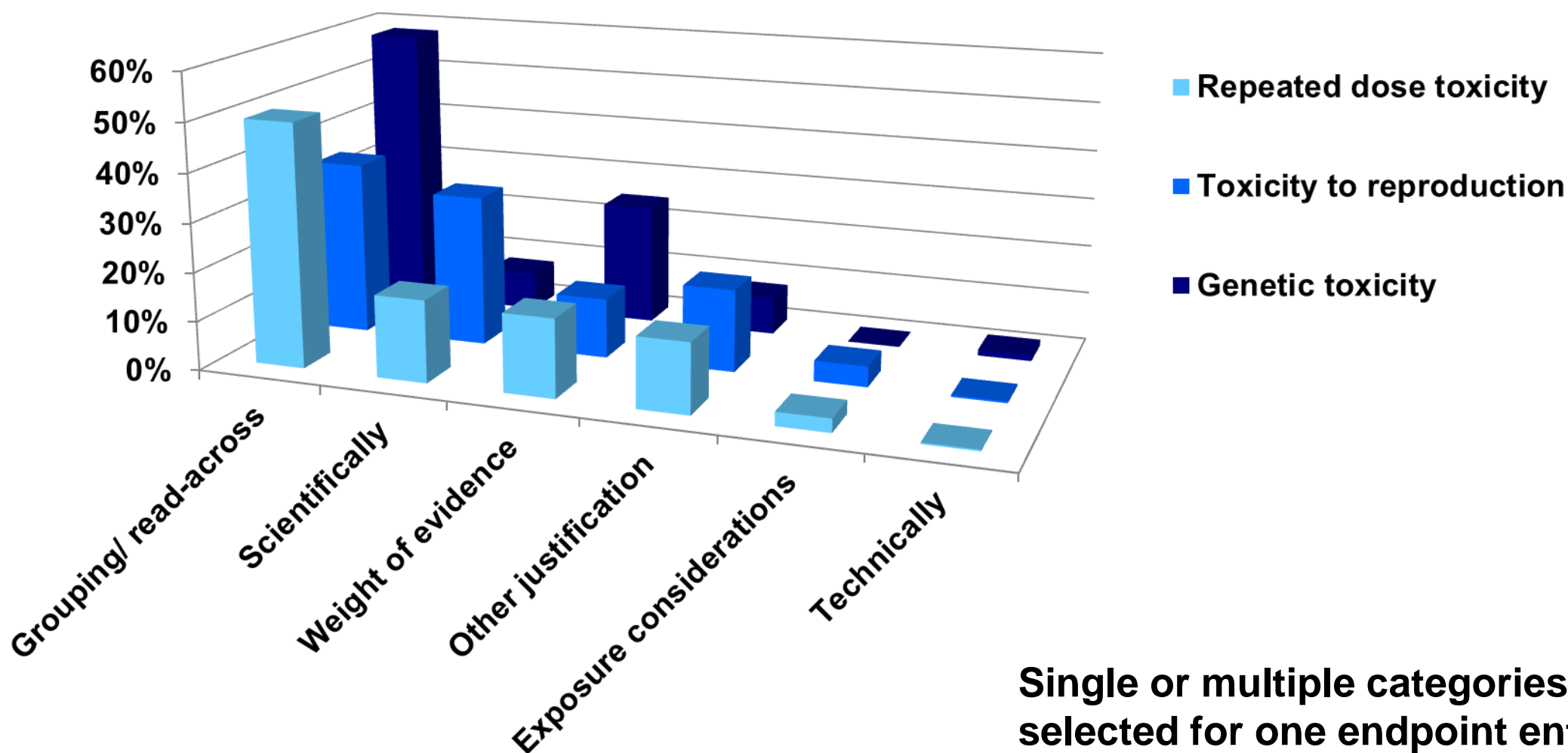
## 5. General Reasons for the Decision 'Non-compliant'

**Given as % of all dossiers with the decision 'non-compliant' for each endpoint**



## 6. Adaptation / Waiver Categories in 'Complex' Cases

- **As selected by the registrants in IUCLID**
- **Given as % of the total number of adaptations / waivers for each endpoint**



Single or multiple categories selected for one endpoint entry

## Summary

- Decision 'profile' different for each human health endpoint
- Less than 25% of the dossiers were 'compliant' for an endpoint
- For the majority of dossiers standard information were adapted / waived ('complex')
- Grouping / read-across most frequent adaptation
- A considerable number of cases was assigned 'non-compliant'
- Major reasons for 'non-compliance'

Registrants did not adapt standard information *or*

Registrants did not provide a justification for data waiving

Test material did not correspond to registered substance

No reference to an appropriate guideline

**Thank you for your attention**

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