GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR
Bundesinstitut für Risikobewertung

REACH Compliance Project "Availability of Health and Environmental Data for High Tonnage Chemicals under REACH" – Data quality of human health data in registrations

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Introduction

- Registration under REACH requires information for hazard and risk characterisation
- Registrant to provide **toxicological and eco-toxicological data**

►C1 REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 18 December 2006

concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

- Standard data requirements in REACH Annexes VII – X (Column 1)
  - Increasing with tonnage

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.6.2. Sub-chronic toxicity study (90-day), one species, rodent, male and female, most appropriate route of administration, having regard to the likely route of human exposure.	8.6.2. The sub-chronic toxicity study (90 days) does not need to be conducted if: — a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure, or

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- Standard data requirements in REACH Annexes VII – X (Column 1)
  - Increasing with tonnage
- Deviations possible according to specific rules
  - Data waiving (Column 2)
  - Adaptation/alternative data (Annex XI)

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Methodology

Methodology

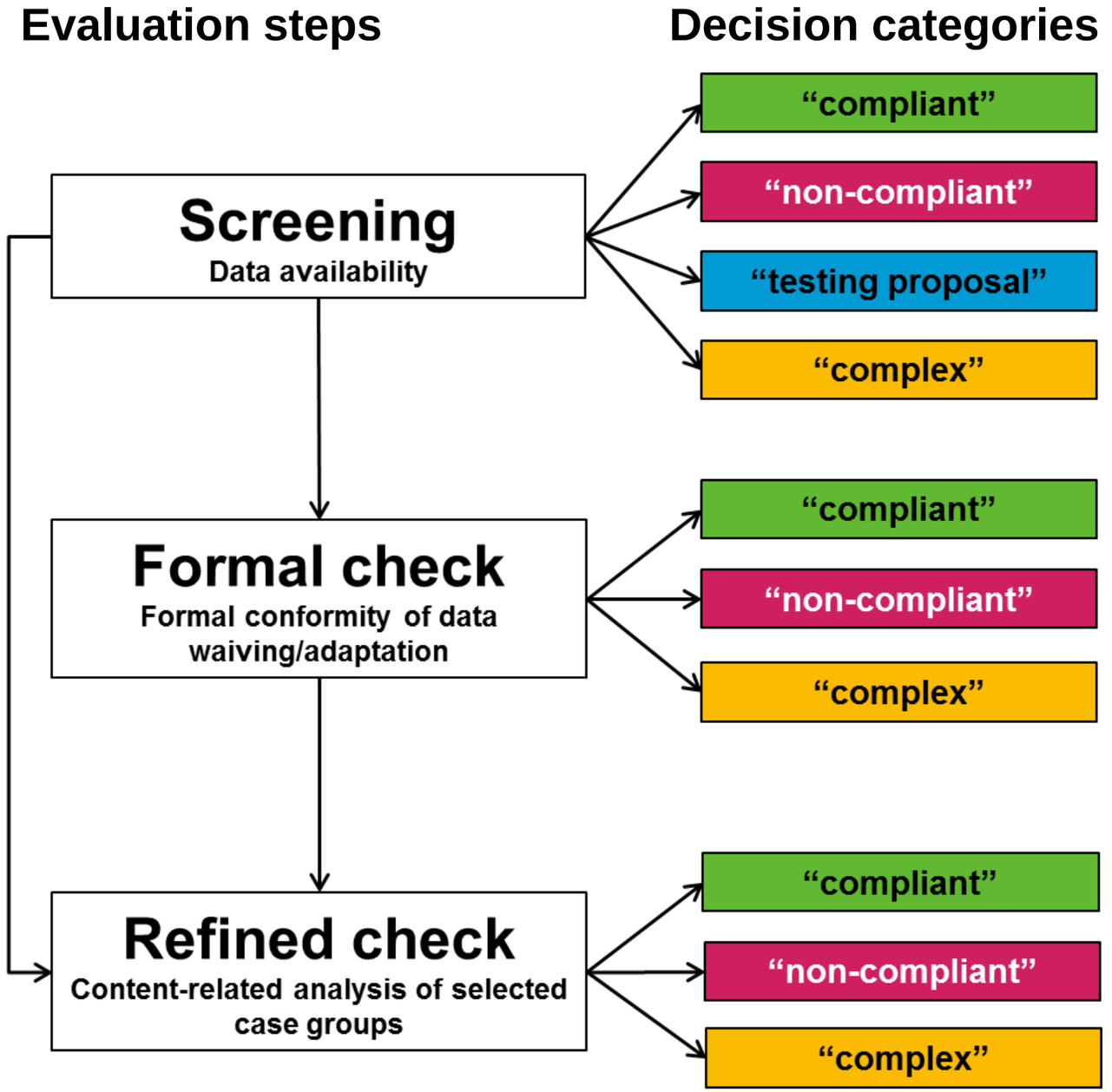
Endpoints

Human health:

- Repeated dose toxicity (RDT)
- Mutagenicity (Muta)
- Developmental toxicity (DevTox)
- Reproductive toxicity (ReproTox)

Environment:

- Abiotic degradation (AbioDeg)
- Biotic degradation (BioDeg)
- Bioaccumulation (Bioaccu)
- Ecotoxicity (Ecotox)
- Environmental exposure



Methodology

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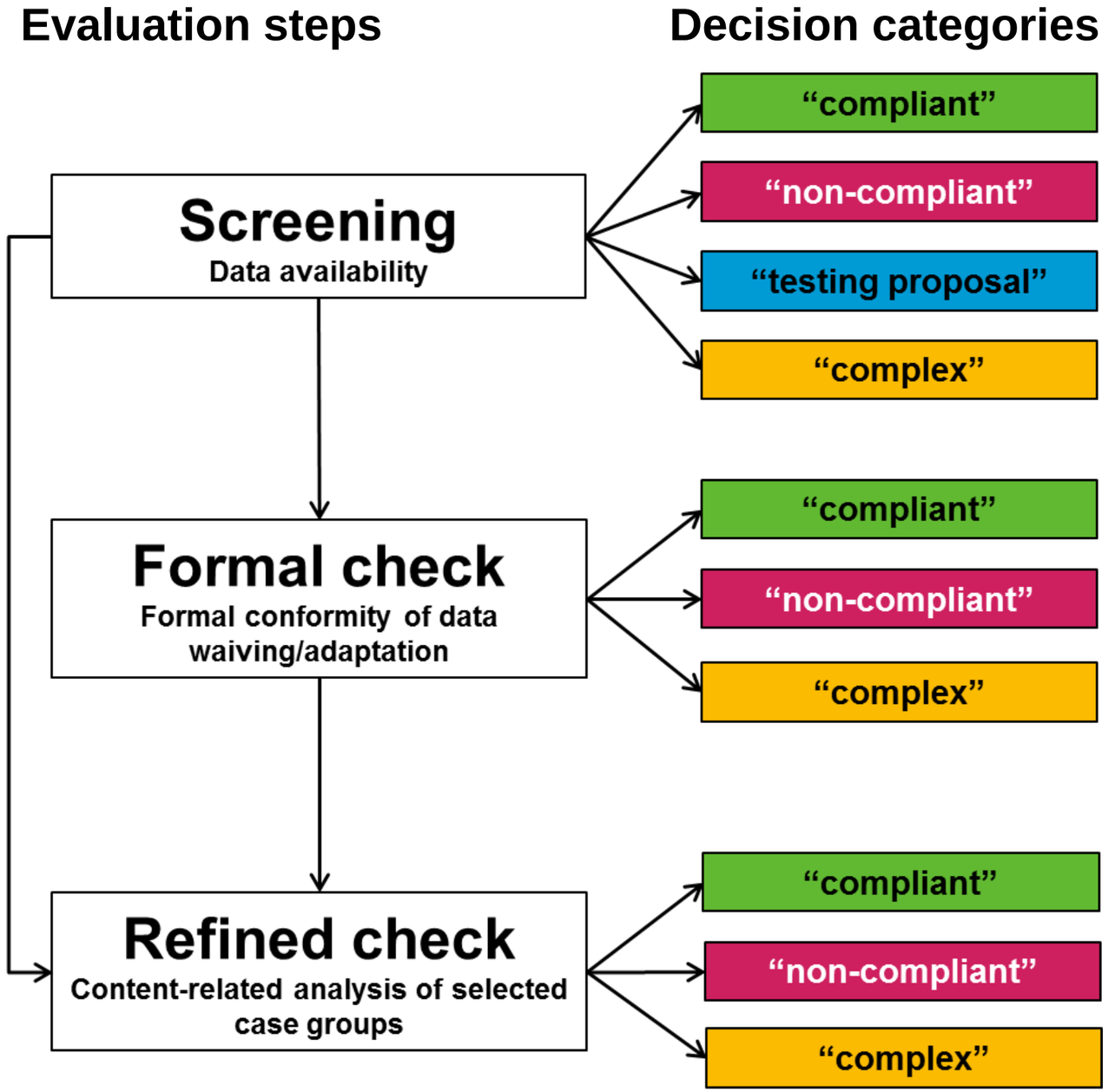


Methodology – Decision categories

“Compliant”	Available standard information or waiving/adaptation **complies with** the formal criteria of REACH Annexes VII-XI.
“Complex”	A final assessment of conformity with REACH Annexes VII-XI is not possible within the scope of the project.
“Non-compliant”	Available standard information or waiving/adaptation **does not comply** with the formal criteria of REACH Annexes VII-XI.
“Testing proposal”	A testing proposal is provided to fulfill the information requirements (assessed as “compliant”).

To note: **Methodology differs from Compliance Check according to REACH Article 41.**

Methodology – Screening on all dossiers

- Decision trees on standard information requirements
- ECHA support: Database extraction
- If waiving/adaptation is available:
  - Documentation of respective categories

Example Repeated Dose Toxicity (RDT)

Question 2:

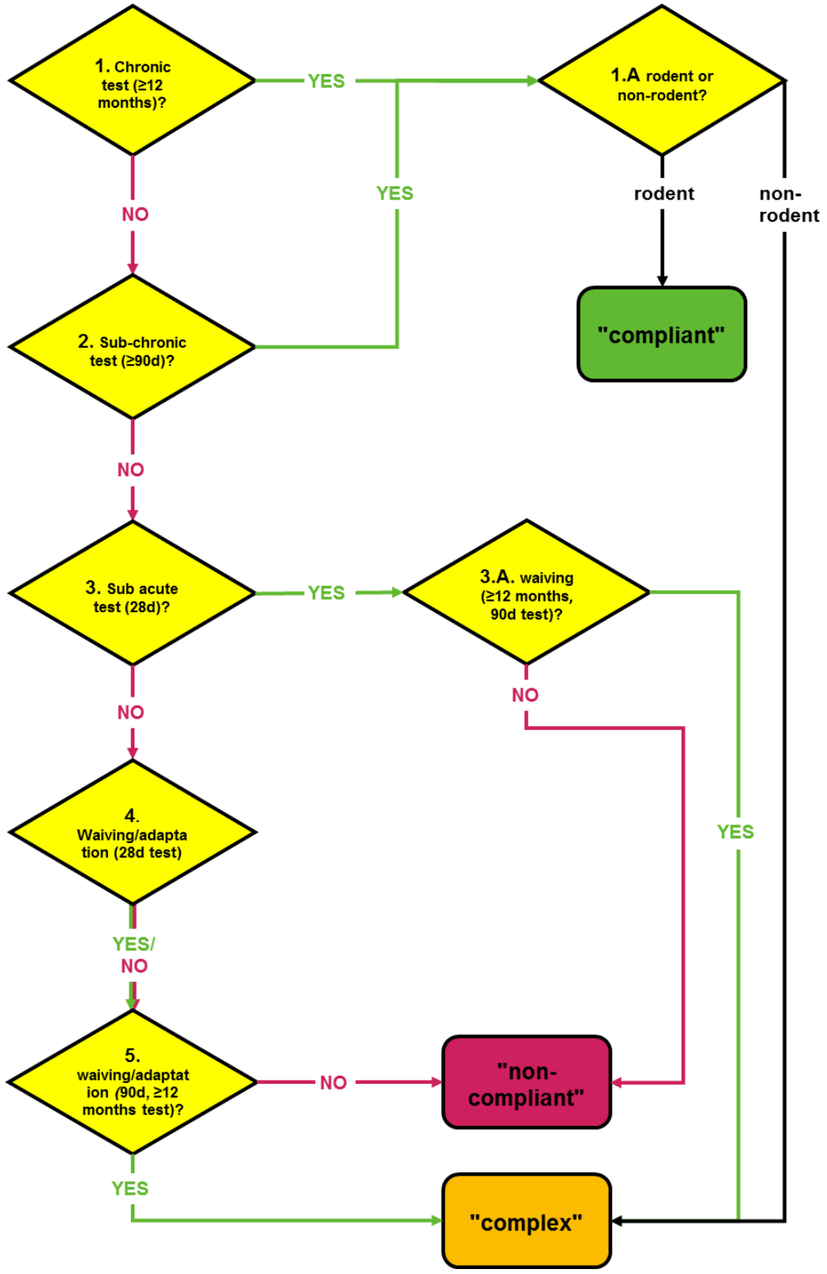
Is a subchronic test available?

- **Yes** → 1a
- **No** → 3

Question 1a:

Is the subchronic test conducted on rodents or non-rodents?

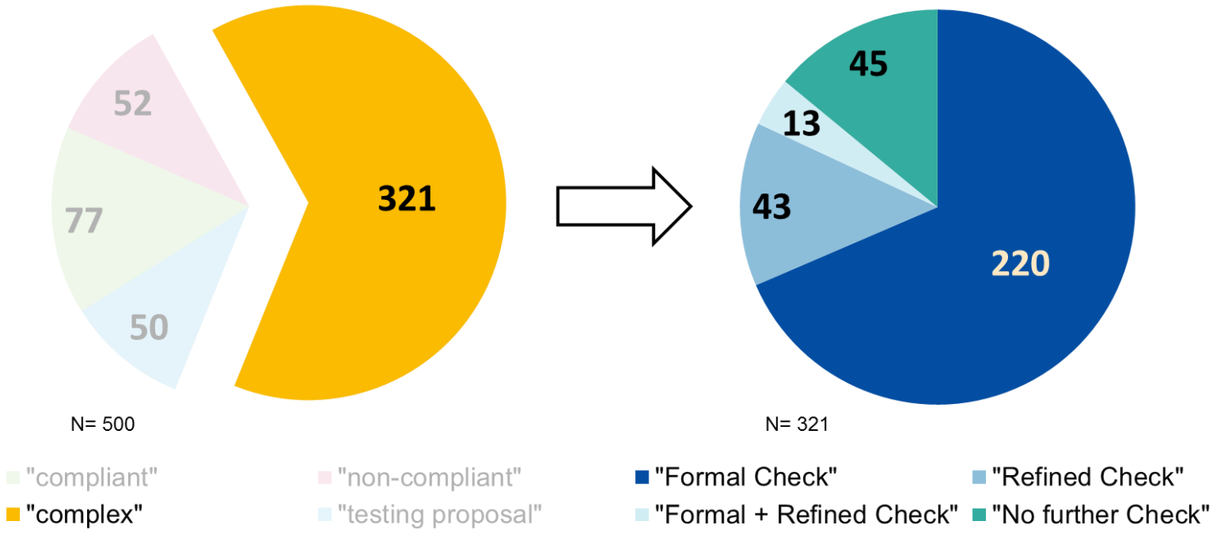
- **Rodents** → "compliant"
- **Non-rodents** → without conclusion ("complex")



Methodology – Further check on “complex” cases

- 100-1000 tpa: Random sample of 500 dossiers
- ≥1000 tpa: All dossiers

Example



Formal check on data waiving and adaptation

- Grouping of substances /Read Across (RA)
- Qualitative or Quantitative structure-activity relationship ((Q)SAR)
- Testing technically not possible (tech)
- Substance tailored, exposure-driven testing (expo)
- Endpoint specific data waiving (Column 2)

Refined check on data waiving and adaptation

- Weight of Evidence (WoE)
- Data waiving (selected case groups)

Formal check and Refined check

- Dossier contains e.g. RA and WoE

No further check

- Only non-standard test methods available → complex

Methodology – Formal Check

Standard questions to check formal conformity with REACH Annexes VII – XI

Example:

Read Across

1. Justification according to Annex XI 1.5.?
2. Key study?
3. Exposure duration?

Question 1	Question 2	Question 3
no = non-compliant	**no = non-compliant**	**no = non-compliant** **unclear = without conclusion**
Is a justification according to Annex XI 1.5, paragraph 2 given? (or other adequate explanation)	**Is a key study with reliability 1 or 2 available?**	**Is the exposure duration comparable or longer?**
Similarities based on (1) functional group or (2) precursors, breakdown products or (3) constant pattern in the changing of potency		

Methodology – Refined Check

Asssessment with specific approaches

No.	Question	Assessment criteria
1	Is more than one independent piece of information available?	▪ Endpoint study records - Weight of evidence studies - Key studies - Supporting studies - Other information ▪ Endpoint summary
2	Is data waiving incorrectly flagged as WoE?	▪ Justification for data waiving
3	Is one piece of information obviously sufficient on a stand-alone basis?	▪ Study with rel. 1 or 2 ▪ Study considered equivalent or similar to the standard test method ▪ No conflicting results from other studies
4	Is a WoE summary available?	▪ Endpoint summary ▪ ESRs ▪ CSR ▪ Attachments
…		

Is a WoE-summary available?

Weight of Evidence (WoE, Annex XI 1.2)

- Consideration of several independent sources that would be not sufficient on stand alone basis

Other remaining cases/case groups after formal check that need in-depth/content analysis

- Examples
  - ReproTox: Trigger to identify
  - Data waiving refers to Chemical Safety Assessment (e.g. Ecotoxicity)

Results
Human Health
Endpoints

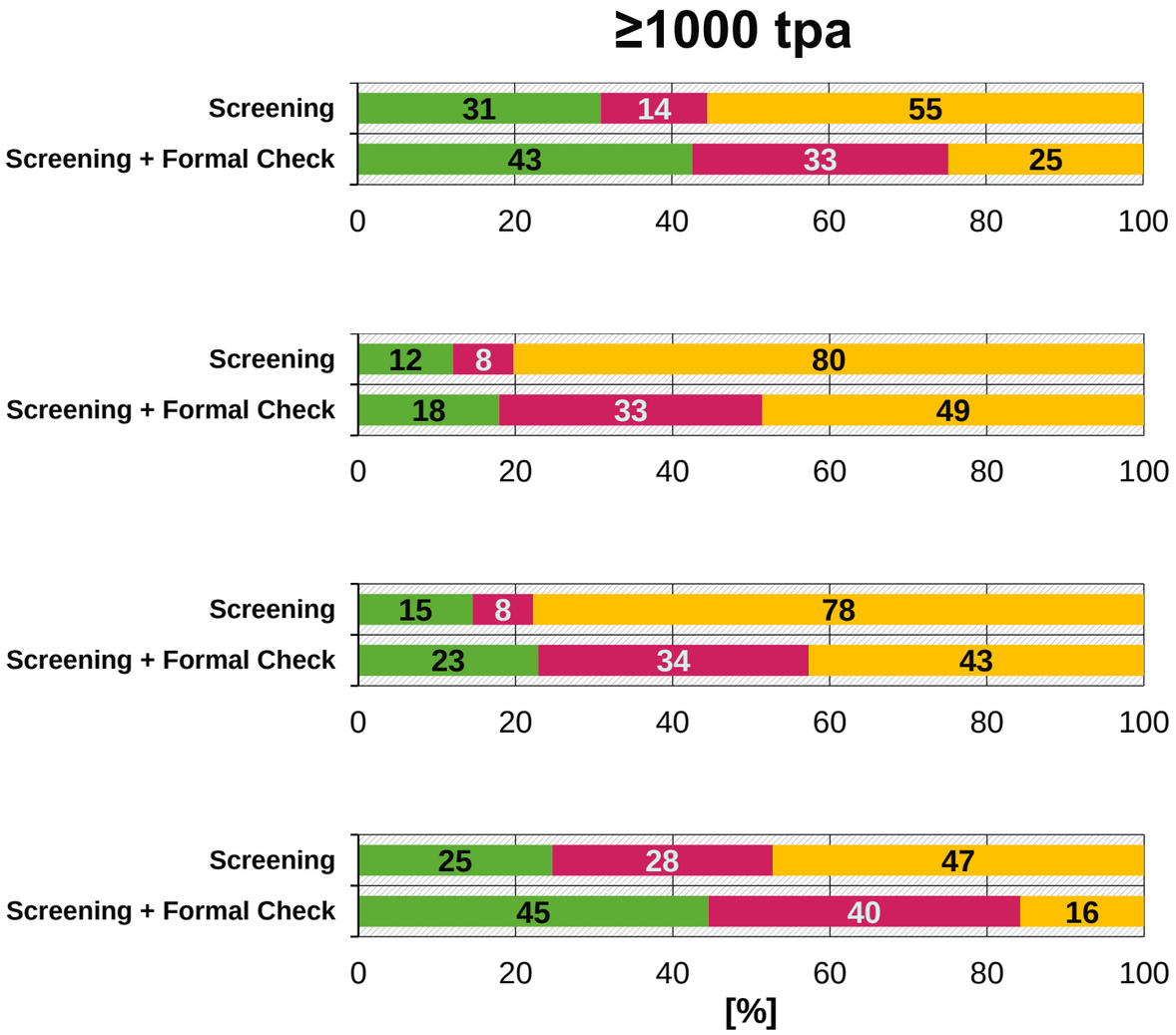
Human health endpoints – Results after screening and formal check

Repeated dose toxicity

Developmental toxicity

Reproductive toxicity

Mutagenicity



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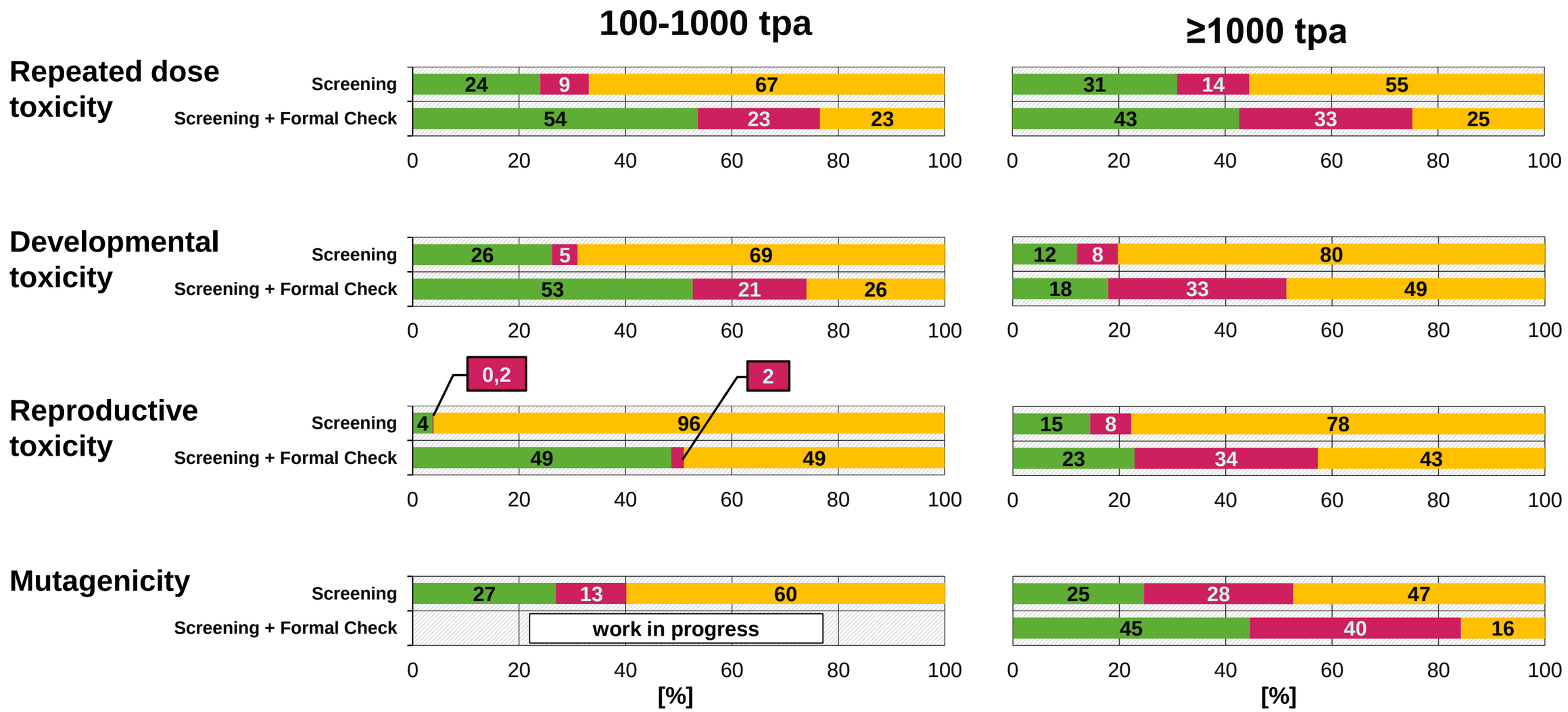
Human health endpoints – Results after screening and formal check



Results – Developmental toxicity

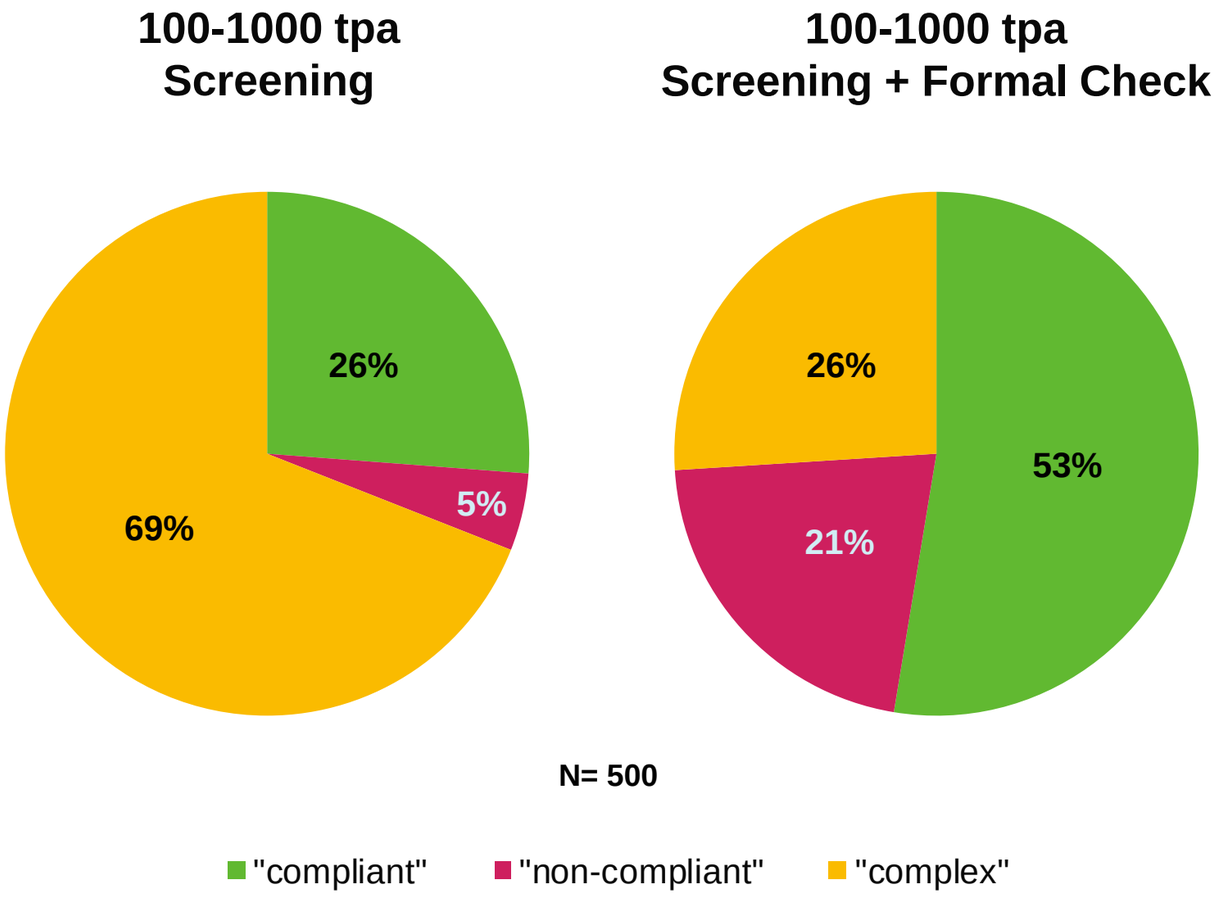
Main assessment criteria

- Availability of a prenatal developmental toxicity study (OECD Test Guideline 414)

100 – 1000 tpa:

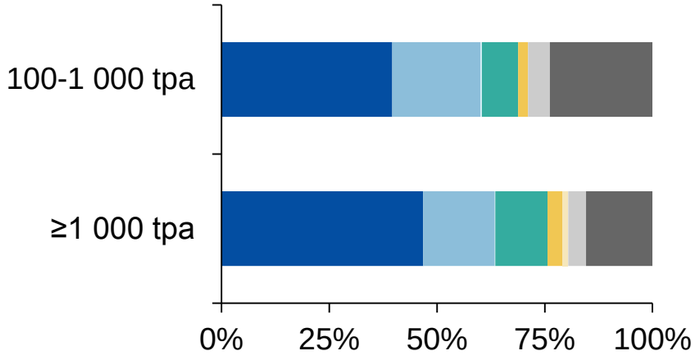
- 26 % “compliant” (TG 414 available or testing proposal)
- Data gap (5%)
- Waiving/adaptation (69%)

→ Majority of registrants used options to avoid animal testing

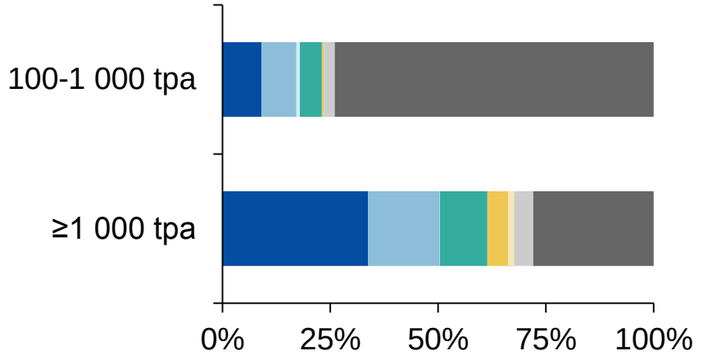


Results –
Frequency of documented data waiving/adaptation categories

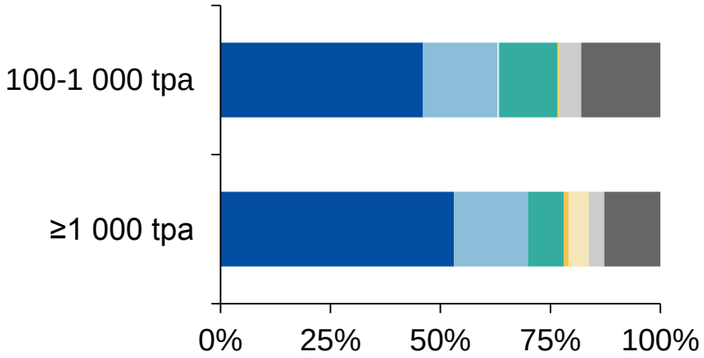
Developmental toxicity



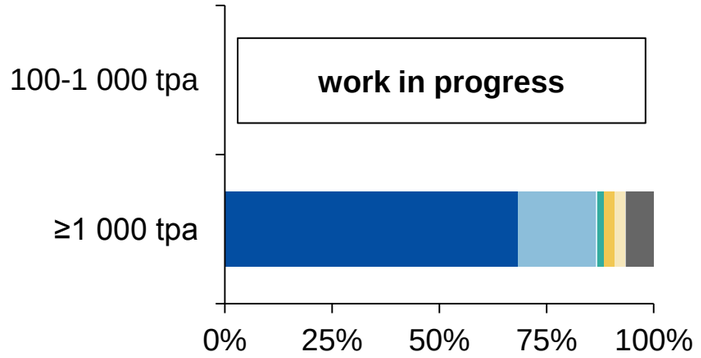
Toxicity to reproduction



Repeated dose toxicity



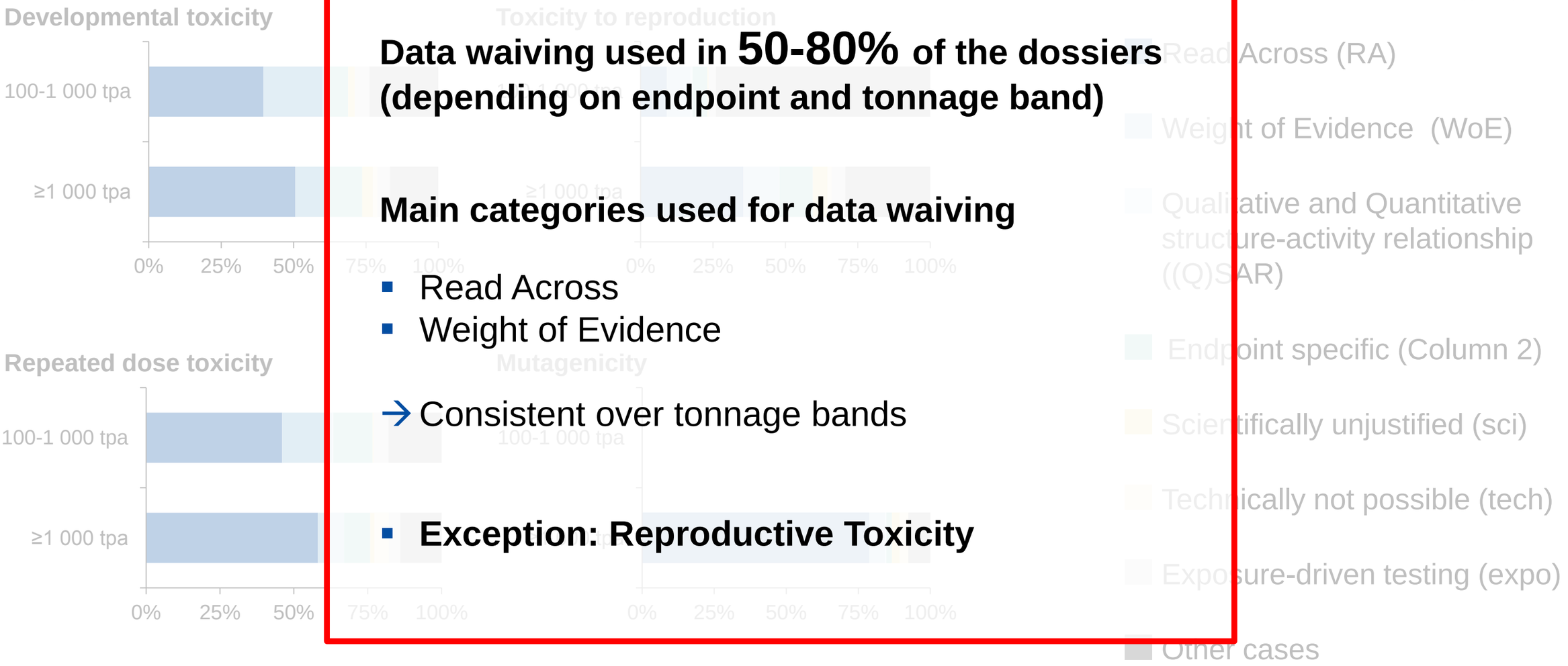
Mutagenicity



Waiving/adaptation category

- Read Across (RA)
- Weight of Evidence (WoE)
- Qualitative and Quantitative structure-activity relationship ((Q)SAR)
- Endpoint specific (Column 2)
- Scientifically unjustified (sci)
- Technically not possible (tech)
- Exposure-driven testing (expo)
- Other cases

Results –
Frequency of documented data waiving/adaptation categories



Data waiving used in 50-80% of the dossiers (depending on endpoint and tonnage band)

Main categories used for data waiving

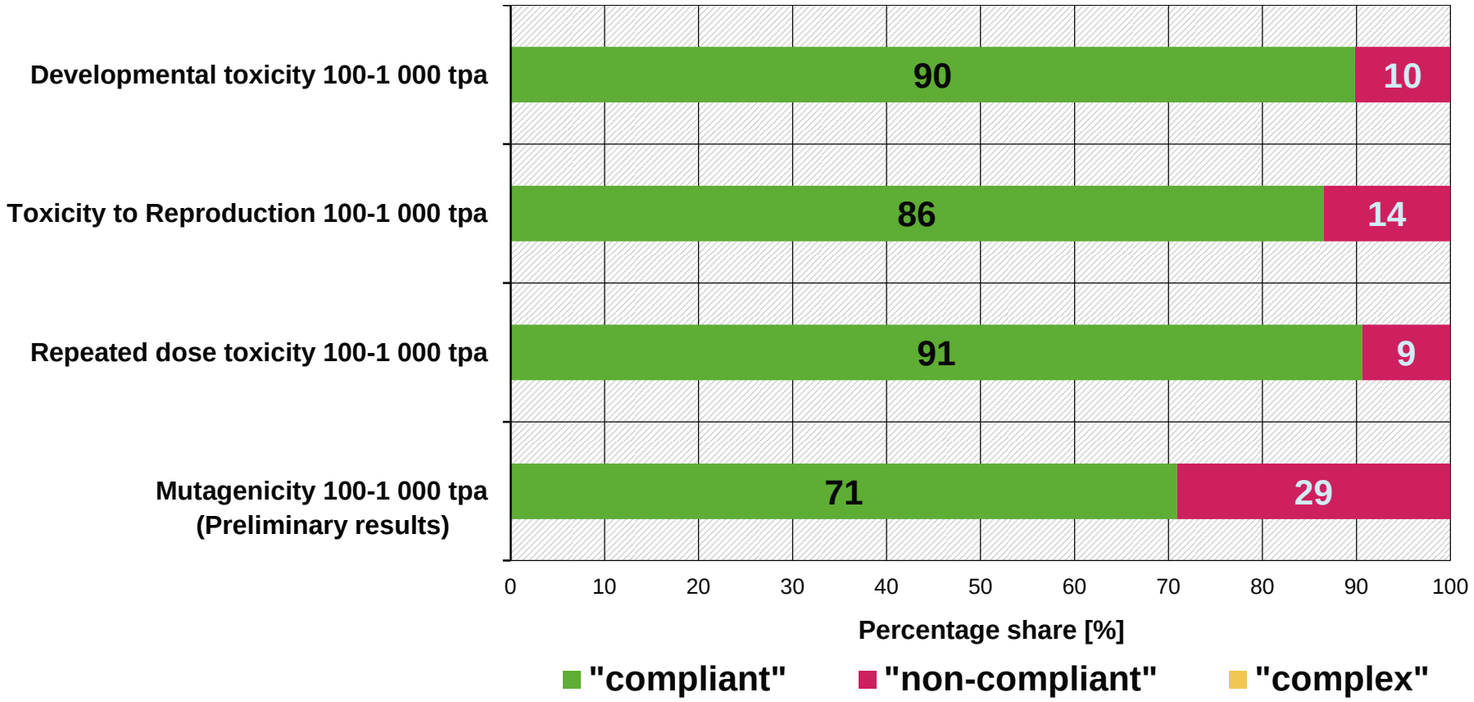
- Read Across
- Weight of Evidence

→ Consistent over tonnage bands

- **Exception: Reproductive Toxicity**

* WoE: number in ≥ 1000 tpa may be higher due to differences in documentation

Results –
Formal Check: Read Across (RA)



Main assessment criteria

Is a justification according to Annex XI 1.5, paragraph 2 given? (or other adequate explanation)
Similarities based on (1) functional group or (2) precursors, breakdown products or (3) constant pattern in the changing of potency

Annex XI, 1.5 – Grouping of substances and RA approach

→ **On average, 85% of RA/grouping approaches were <u>formally</u> “compliant”**

→ **Scientifically, RA not assessed in this project**

Results –
Formal Check: Read Across (RA)

Reasons for non-compliance

- Justification not available/not sufficient
- RA-substance not included in category approach
- Main constituents are not considered

ECHA
EUROPEAN CHEMICALS AGENCY

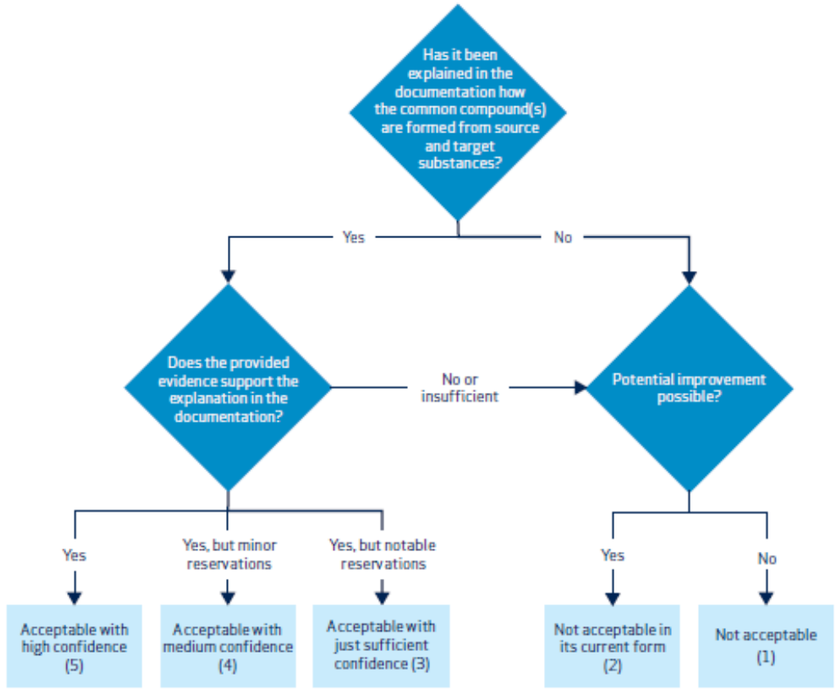
Read-Across Assessment Framework (RAAF)

https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

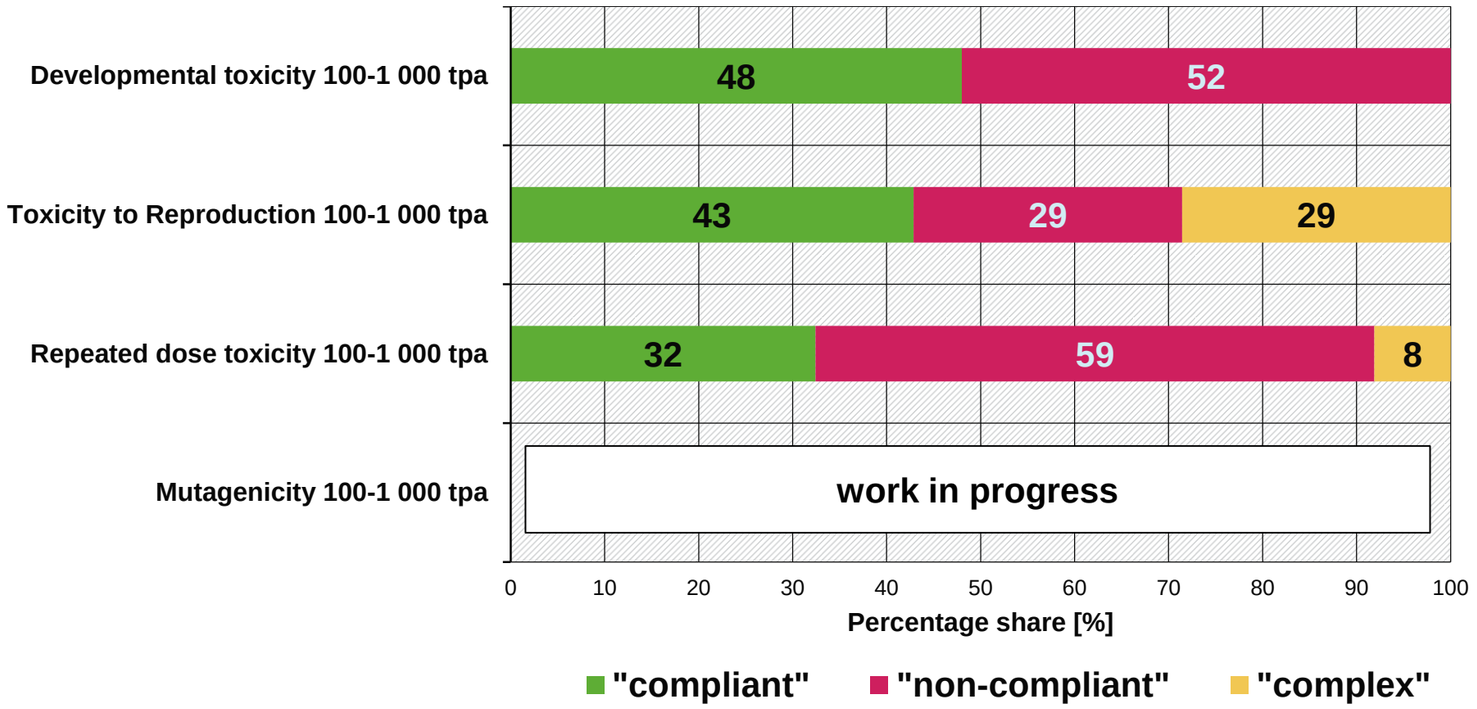
Recommendation

RA justification based on different lines of evidence

- Considers the registered substance and the RA-substance
- Structural similarity and differences
- Similarity of toxicity pattern
- Toxicokinetic information to support the RA hypothesis



Results –
Formal Check: Endpoint specific waiving (Column 2)



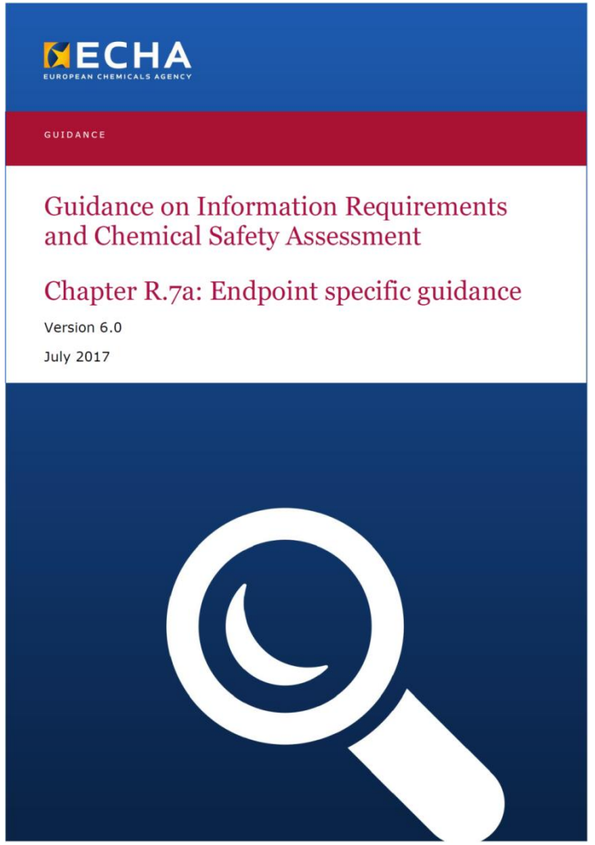
Main assessment criteria
RDT

Is Annex IX 8.6.2 column 2, bullet point 1 referenced and the respective justification given (all criteria explained)?
(1) Reliable 28-day study is available **and** (2) 28-day study shows severe toxicity according to criteria for classification as R48 **and** (3) NOAEL 28-day allows extrapolation of NOAEL 90-day for the same route of exposure

All three criteria must be explained!

→ **On average, 47% of waivings according to Column 2 are “non-compliant”**

Results –
Formal Check: Endpoint specific waiving (Column 2)



Reasons for non-compliance

- Not all criteria were addressed
- Frequent argumentation: Lower tier studies (e.g. screening or 28-day studies) showed no endpoint specific toxicity

Recommendation

- Each data waiving requires adequate justification
- Justification on **all three** criteria of column 2, 3rd bullet needed:

  "substance is of **low toxicological activity** […], **no systemic absorption** occurs via relevant routes of exposure […] ***and*** there is **no or no significant human exposure**." (Example: DevTox)

- Subtle (adverse) effects or the lack of effects in the 28-day/screening study require further testing if the studies are **not** sufficient for classification and risk assessment

Special case – Reproductive Toxicity

≥1000 tpa:

- EOGRTS/ OECD TG 443 is a standard data requirement

→ Waiving according to Annex X 8.7.3.; Column 2 or Annex XI neccessary

100-1000 tpa:

- EOGRTS/ OECD TG 443 is only required if:

„ the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TG 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity“ (Column 1 of Annex IX 8.7.3)

→ **Study needs a trigger**

→ Waiving informative, but formally not required (Column 1 argument)

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.7.. Extended One-Generation Reproductive Toxicity Study (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.	8.7.3. An Extended One-Generation Reproductive Toxicity Study with the extension of cohort 1B to include the F2 generation shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if: (a) the substance has uses leading to significant exposure of consumers or professionals, taking into account, inter alia, consumer exposure from articles, and (b) any of the following conditions are met: — the substance displays genotoxic effects in somatic cell mutagenicity tests *in vivo* which could lead to classifying it as Mutagen Category 2, or — there are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, or — there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches.

EOGRTS: extended one-generation reproductive toxicity study

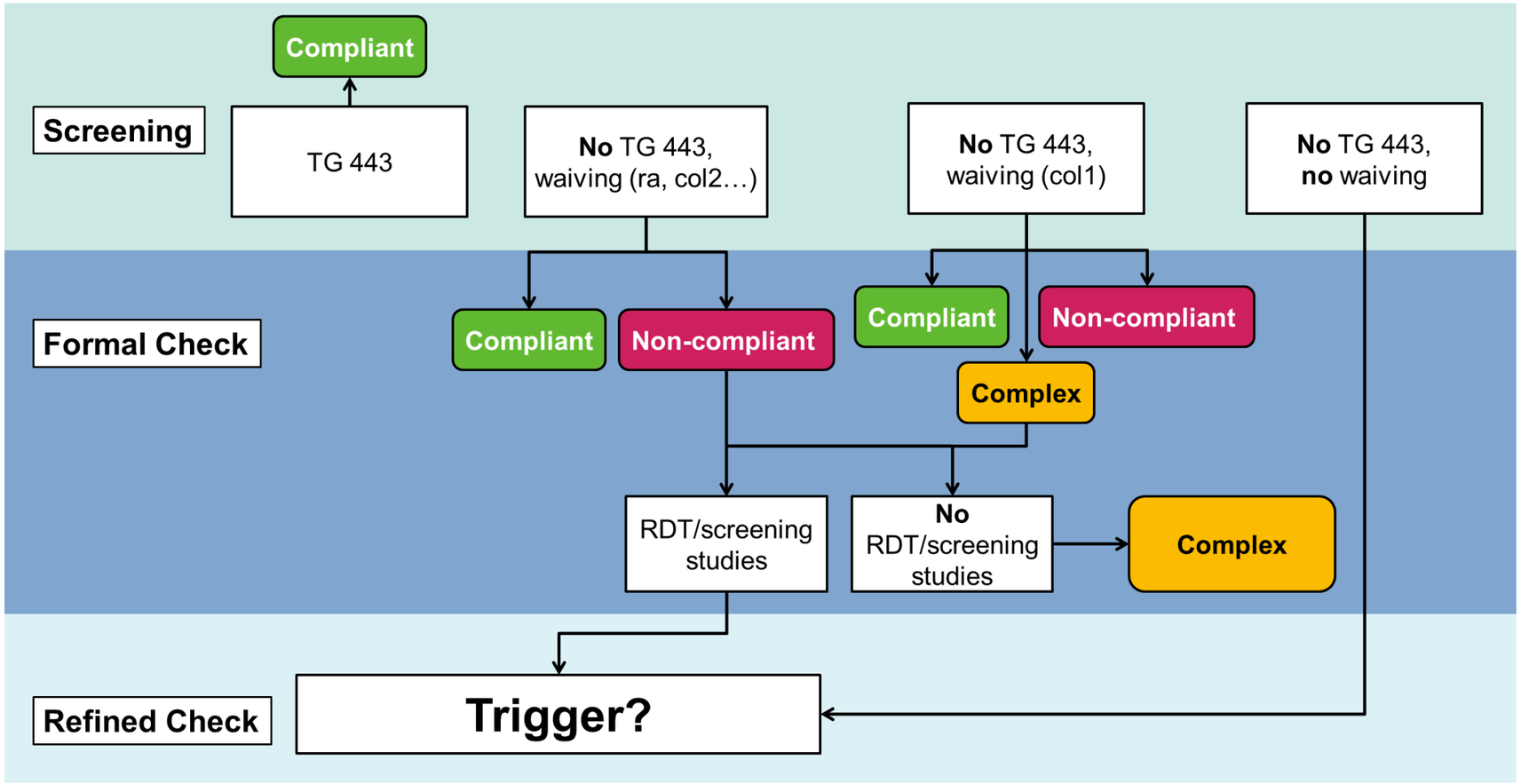
Methodology –
Reproductive toxicity: Screening and Formal check (100-1000 tpa)

Main assessment criteria:

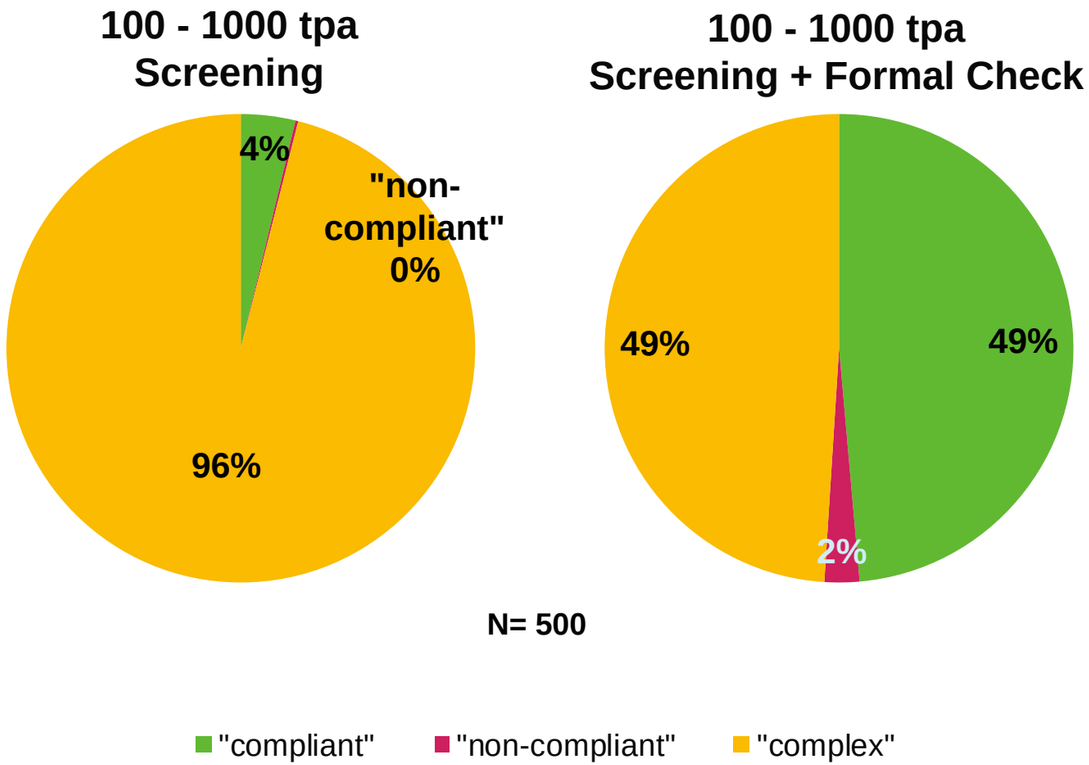
- EOGRTS has to be done if RDT – studies indicate adverse effects on reproduction (trigger)

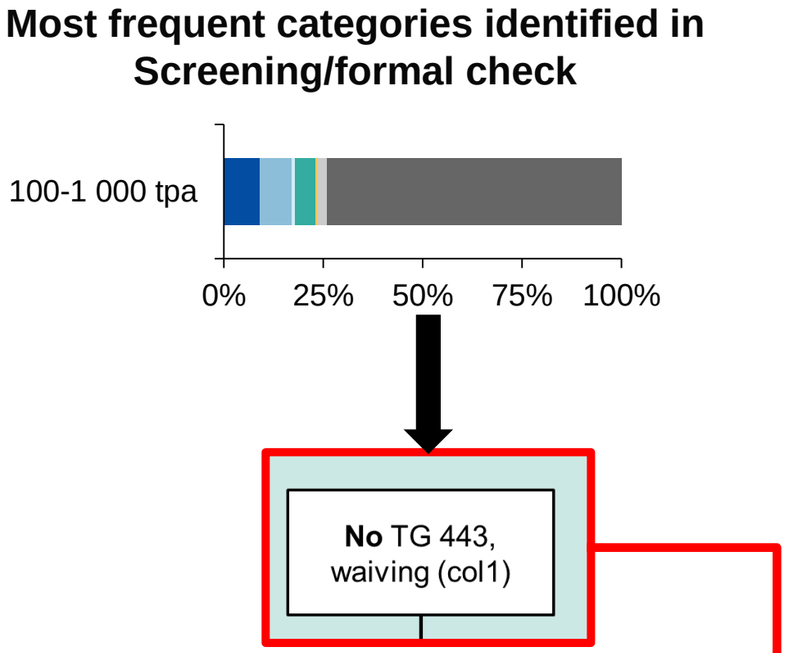
→ Trigger (examples):

  - Reduced mating, fertility or litter size
  - Changes in reproductive organ weight



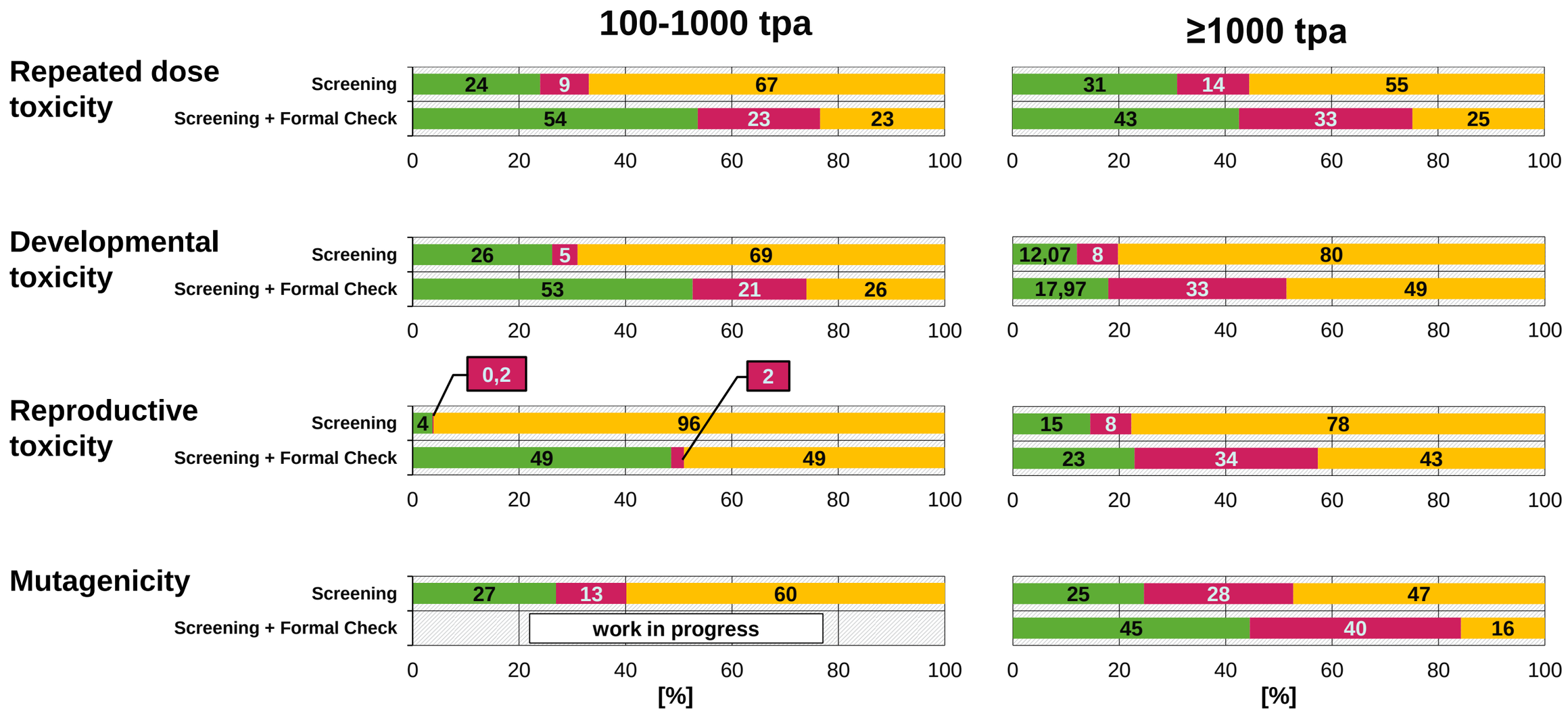
Results –
Reproductive toxicity: Screening and Formal check (100-1000 tpa)





- **96% dossiers were “complex” after screening because they have no study AND no waiving or waiving/adaptations**
- **Decreased to 49% after formal check**
- **Col1 waivings are 70% “compliant” (appropriate justification: no Trigger in RDT/screening studies)**

Human health endpoints – Results after Screening and Formal check



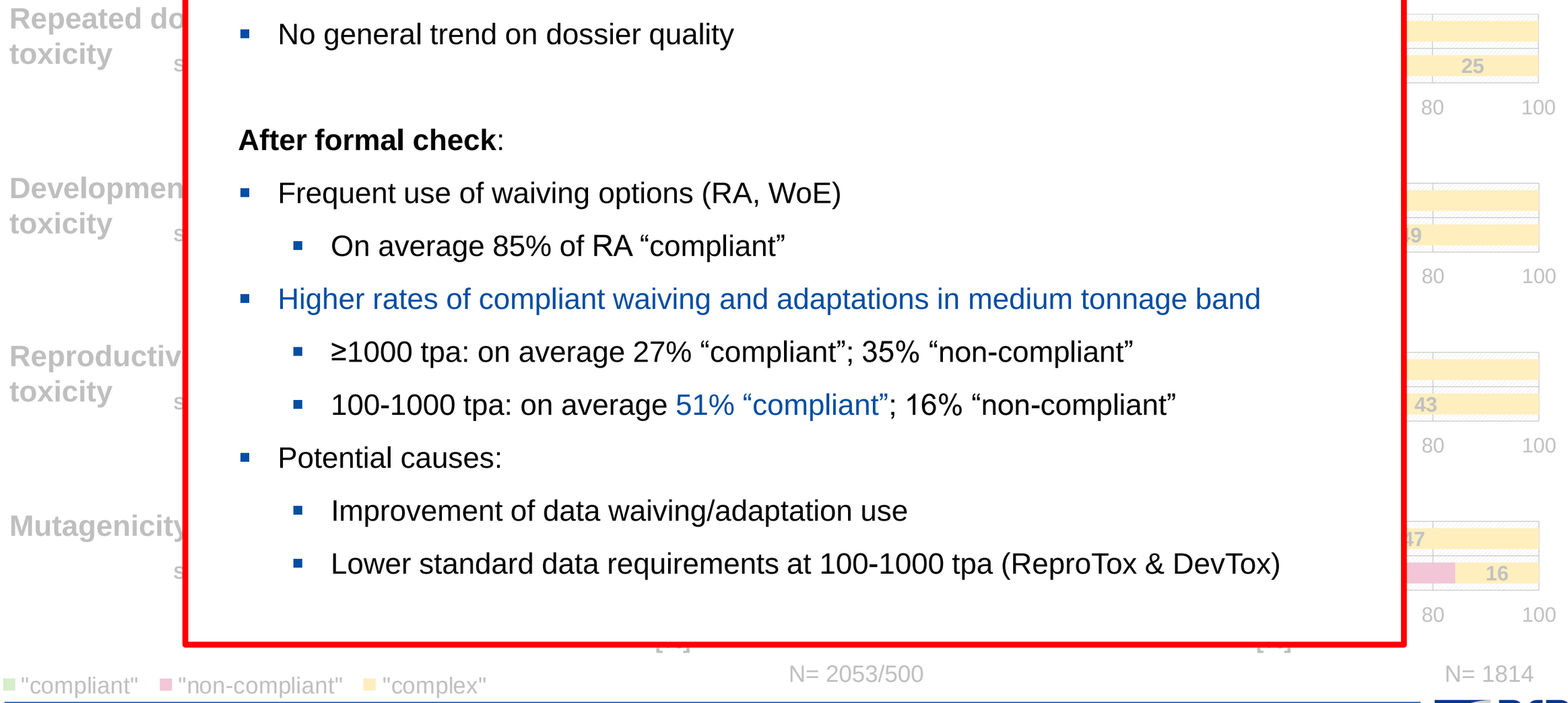
Human health endpoints – Results after Screening and Formal check

After screening of 100-1000 tpa and ≥1000 tpa

- No general trend on dossier quality

After formal check:

- Frequent use of waiving options (RA, WoE)
  - On average 85% of RA “compliant”
- Higher rates of compliant waiving and adaptations in medium tonnage band
  - ≥1000 tpa: on average 27% “compliant”; 35% “non-compliant”
  - 100-1000 tpa: on average 51% “compliant”; 16% “non-compliant”
- Potential causes:
  - Improvement of data waiving/adaptation use
  - Lower standard data requirements at 100-1000 tpa (ReproTox & DevTox)



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Thank you for your attention

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Outlook –
Refined Check: Toxicity to reproduction – „Trigger“

From a screening study or equivalent:

- Changes in reproductive or other endocrine organ weight in intact animals
- Effects in spermatogenesis or folliculogenesis in vivo and/or histopathological findings in reproductive organs and/or accessory sex organs
- Effects in histopathology of the thyroid
- Effects on sperm parameters analysis or oestrous cycle
- Biologically relevant changes in hormone levels in vivo (related to reproductive toxicity)
- Reduced mating, fertility or litter size
- Increased incidence of abortions compared to controls
- Changes in gestation length
- Reduced survival of offspring
- Reduced body weight of offspring independent of litter size
- Reduced maternal care
- Changes in anogenital distance unrelated to body weight/size
- Changes in nipple retention
- Indication of other endocrine disrupting modes of action related to reproductive toxicity.

From a repeated dose toxicity study:

- Changes in reproductive or other endocrine organ weight in intact animals
- Effects in spermatogenesis or folliculogenesis in vivo and/or histopathological findings in reproductive organs and/or accessory sex organs
- Effects on sperm parameters analysis or oestrous cycle
- Biologically relevant changes in hormone levels (related to reproductive toxicity)
- Indication of other endocrine disrupting modes of action related to reproductive toxicity

From *in vivo* studies from non-intact animals (if the findings are considered relevant for intact animals/humans):

- Changes in reproductive or other endocrine organ weight
- Indication of other endocrine disrupting modes of action related to reproductive toxicity