EUROPEAN MEDICINES AGENCY

5th meeting NIOG-Industry

Update on new approaches on AI determination for nitrosamines

New Carcinogenic Potency Categorisation Approach (CPCA) and Enhanced AMES Test (EAT) - **Overview**

- New **CPCA**, allows 4 categories, ***up to 1.5 µg/day***
  - *E.g.~30 of 50 AIs categorised are at 1.5 µg/day level, additional 11 are at 400 ng/day level*
- **EAT** can be used to support non-mutagenicity, if designated CPCA AI is considered to be too conservative – ***then control at 1.5 µg/day***
- CPCA and EAT are ***long term approaches***, not just interim, and apply to ongoing applications and authorised products
- CPCA and EAT **developed with international partners**, not just EU
- Further options available when NAs limits still not met
  - ***LTL during CAPA implementation for authorised products*** (Q&A22)

  OR:
  - ***NMEG*** (authorised products)
  - ***In vivo test*** (authorised products/ongoing applications)

What is the *new* Carcinogenic Potency Categorization Approach (CPCA) for AI setting?

- New, **science-based** approach to setting AIs more **quickly**
- Underlying principles:
  - Subdivision in potency categories of known Nitrosamines with carcinogenicity data
  - 5 categories:

Category	AI
1	18 ng/day
2	100 ng/day
3	400 ng/day
4/5*	1500 ng/day

*Category 4: may be metabol cally activated but are predicted to be of low carcinogenic potency.
Category 5: are not predicted to be metabolically activated or to react with DNA.

Estimated time for AI assessment with category approach:

- AIs will be set using agreed algorithms obviating the need for extensive discussions, internally and with international partners
- Only when the Applicant/MAH cannot meet the category AI, do additional data need to be submitted and assessed, requiring additional time

All NAs (ca 50) waiting for establishment of AIs have been categorised by NSOEG and published in update of Q&A

Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation QA10 revision 16 (europa.eu)

What is the *enhanced* Ames test?

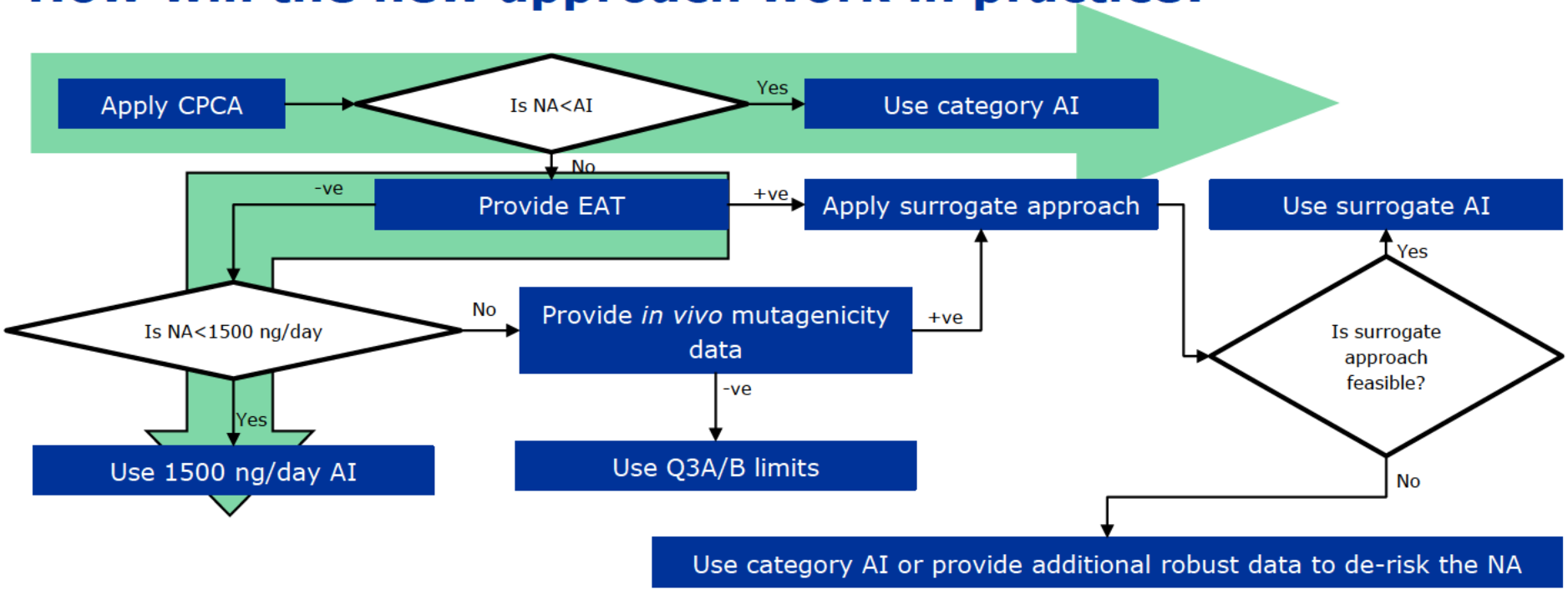
Standard Ames test can be insufficiently sensitive for nitrosamine impurities, hence:

- Revised Ames test protocol with conditions adapted specifically for nitrosamines (sufficiently trustworthy to use for regulatory decision making)
- A negative result in an "enhanced" Ames test **would allow long term control of NA at 1.5 µg/day**
- The new Ames test protocol has been **developed with international partners**
- New protocol published as annex 2 of the updated Q&A
  - Nitrosamines EMEA-H-A5(3)-1490 - QA Art. 5(3) Implementation QA10 revision 16 (europa.eu)

How will the new approach work in practice?

- AI will be established using CPCA (if no compound-specific data are available)
- If NA levels <AI – the AI from CPCA can be used in specification (if applicable, note if levels are <10% AI, then no need to include in spec.)
- If NA levels>AI
  - negative EAT can allow control at 1.5 µg/day
  - positive EAT – surrogate read-across approach can be applied
- If NA levels>1.5 µg/day
  - negative *in vivo* mutagenicity study can allow control as a non-mutagenic impurity (class 5 in ICH M7)
  - positive *in vivo* mutagenicity study – surrogate read-across approach can be applied

How will the new approach work in practice?



Flowchart for illustration purposes only as an example of how the new approach may work, not intended as a complete representation of all scenarios

What happens if the AI limits cannot still not be met?

Treatment duration	Up to 12 months	>12 months up to 10years
Interim limit	13.3 x AI*	6.7xAI*

*In any case the limit should not exceed 1.5 µg/day unless the established AI (Table 1, Q10) is > 1.5 µg/day.

Less than life-time approach (LTL)* to be used during CAPA implementation for authorised products

Revision under discussion

If nitrosamines levels above limit with LTL then

EAT to control to 1.5 µg/day

OR

In vivo test to show non-mutagenicity and NA control as non mutagenic impurity

NMEG (Nitrosamine multidisciplinary expert group)

Next Steps

- EMA/CMDh to consider further revision to Q&A and associated templates as a result of the newly established CPCA and EAT
  - Further updates to be provided to industry in due course
- Continued cooperation with international partners
- Considering the maximisation of resources, industry is encouraged to cooperate and share information, as possible, on conducting in vivo or in vitro tests to support toxicological assessment of nitrosamines

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Any questions?

Further information

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