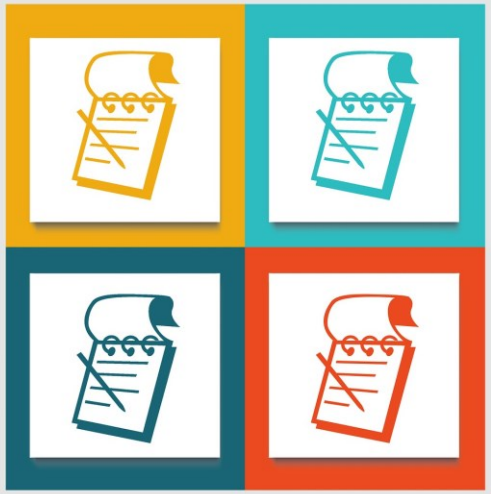
This presentation summarises the results obtained by the participants of

Workshop 2

Quantitative assessment of genotoxic compounds in the absence of data from carcinogenicity studies

It does not necessarily reflect the opinion of the BfR.



RESULTS WORKSHOP 2

Quantitative assessment of genotoxic compounds in the absence of data from carcinogenicity studies

Key question 1

Under which circumstances is a quantitative interpretation based on genotoxicity data already considered?

- For the derivation of HBGV for aneugens – limited guidance is available, e.g. by EFSA 2021
- Potency ranking for research/validation purposes (botanical ingredients, PAHs, etc.)
  - MN data in HepaRG cells for pyrrolizidine alkaloids – not yet regulatory accepted
  - Only accepted in some regulatory contexts, e.g. used by FDA for the evaluation of tobacco ingredients
- Sometimes also used in various fields on a case-by-case basis
  - Acceptance is highly dependend on the regulatory area
  - Large variability in use cases and available database
  - Dependence on the risk-benefit-situation
- When a very extensive knowledge on the MoA is available (at the expense of many animal studies), specific MoA (example Viracept)

Key question 2

Which methodologies, approaches and strategies are considered for quantitative assessment of genotoxic compounds in a regulatory context?

- Techniques used /accepted are highly dependend on the regulatory context

- Derivation of HBGV based on MN data for aneugens (e.g. EFSA guidance 2021)
- TTC (although originally based on carcinogenicity data), e.g. EFSA guidance 2019
- PDE for DNA-reactive impurities in drugs (ICH M7)

Key question 3

Why are strategies for quantitative interpretation of genotoxic compounds needed for regulators?

- Having one harmonized hazard charactersation – one substance one assessment – and afterwords drawing different conclusions depending on the regulatory context
- Provide scientifically-sound advice to risk managers, considering all relevant data
  - Better adress potency of different genotoxic compounds
- Advice required to protect the public (and professionals)
- To overcome/address huge differences regarding data requirements and risk assessment currently triggering different outcomes
- Developing harmonised approaches for evaluation substances throughout different legislations

  (one substance one assessment)
- Animal welfare (RRR), Saving resources, Quicker assessment: save carcinogenicity studies

Why are these methodologies not yet implemented into regulatory practice? What are the reasons from the perspective of different legislations?

- Limitations and uncertainties
- Challenges regarding data sharing throughout different regulations

Key question 4

What are feasible strategies for quantitative assessments in the future?

- Why are these methodologies not yet implemented into regulatory practice?
- What are the reasons from the perspective of different legislations?
- What are uncertainties and challenges?
- What are possible solutions for applicability in different legislations?
- What kind of data is needed to ensure human safety?

Key question 4

What kind of data is needed to enable a quantitative interpretation that has a meaning for human health, considering also uncertainties?

- Minimum requirements (no full consensus could be reached – may not convince regulators)
  - Using in vitro data for identifying the relevant endpoint (clastogenicity, aneugenicity, gene mutations)
  - Development of an intelligent strategy for in vivo follow up (appropriate species, relevant tissue etc.)
  - Currently in vivo data can be used for quantitative interpretations, supported by NAMs

- Further data showing that genotoxicity endpoint is generally more sensitive than the cancer endpoint still needed

Availability and suitability of currently available OECD TG methods?

- Guidance documents need adaption

New methods and/or adaptation of existing OECD TGs?

- More dose levels (at least 5?) are needed if data shall be used for quantitative interpretations
- Tiered approach for dose setting to capture the most relevant dose range (takes longer)

What are suitable reference points and how to standardise the procedure (BMD, NOGEL …)?

- BMD modelling is considered as the most appropriate way
- Harmonisation of approaches for BMD modeling (e.g. model selection, model averaging, CES selection)

Key question 4

What kind of data is needed to enable a quantitative interpretation that has a meaning for human health, considering also uncertainties?

AOP and mechanistic information

- Larger uncertainty factors are needed to cover uncertainties unless detailed information on MoA etc. is available
- Default uncertainty factors should be flexible depending on reliable and appropriate data
- Information on the species differences, metabolic differences, critical live stage, target tissue, MoA, and DNA repair would be needed to adapt uncertainty factors
- Support by in silico methods and PBTK modeling – optimization of tools is still needed

Key question 4

What kind of data is needed to enable a quantitative interpretation that has a meaning for human health, considering also uncertainties?

Can we derive toxicological reference points from genotoxicity data?

- This is technically possible. However, there is no consensus on it´s use for deriving HBGV or MOE and whether it is protective for human health.
- An increase in mutation frequency has been linked to adversity.
- The available data suggest that a risk assessment based on genotoxicity data should be protective when predicting carcinogenicity risk. However, further data are helpful, e.g. for covering chemical space. Further data is also helpful to cover also other endpoints.
- There is no overall consensus which approach may be considered in a particular situation, e.g. regarding the shape of the dose-response curve.

Key question 5

What are the next steps?

- Adaption of OECD test guidelines
  - facilitating quantitative analysis and interpretation (more dose levels etc.)
- Development of guidance documents
  - OECD defined approach document aimed for quantitative assessments of genotoxicity data
  - Validation studies to support the acceptance of the concept
- Case studies
  - To clarify the correlation between genotoxic endpoints and downstream effects such as carcinogenicity
- Continued exchange to develop consistent strategies for quantitative risk assessment of genotoxic compounds

Statements from workshop 2

Statement 1

- Risk assessment of genotoxic compounds in the absence of data from carcinogenicity studies have only been acepted in some regulatory fields, yet.

Statement 2

- To broaden the applicability, more in-depth discussion is needed regarding certain aspects:
  - Data requirements (type of data, endpoint, study design, etc.)
  - Result: HBGV or MoE?
  - Suitable uncertainty factors
  - Acceptance from regulatory bodies

Persons presenting workshop results on Wednesday

- Hans-Jörg Martus
- George Johnson