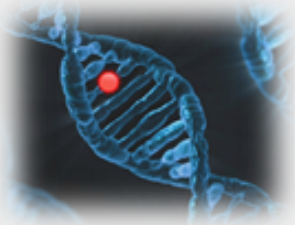
This presentation summarises the results obtained by the participants of

Workshop 1

Risk assessment of genotoxic compounds in the presence of data from carcinogenicity studies

It does not necessarily reflect the opinion of the BfR.



Risk Assessment of Genotoxic Compounds
Challenges and Future Perspectives

Risk assessment of genotoxic compounds

➔ in the presence of data from carcinogenicity studies

RESULTS WORKSHOP 1

Referring to Hazard Identification:

What should be considered as adverse?

- Any interaction may result in an adverse outcome
- Can be seen at any level (molecular, cellular, tissues)
- Effects can be transient or persistent (which may have an impact on the adversity)

What should be considered as initiating event?

- Any molecular initiating event that leads to the known adverse outcome in an AOP
- Any effect may be an initiating effect, that needs to be investigated case-by-case
- Difficult to decide what is initiating if there are different MoA (e.g. genotoxicity and endocrine disruption)

Referring to Hazard Characterisation:

Could it be justified to assume that mutagenic effects have thresholds, based on which information?

Different views:

- Everything may have a threshold, the challenge is to identify it. How many studies, animals, species are required to confirm it?
- There is a network of events and many different MoA. That makes it so complicated
- DNA repair does not always guarantee that there is a threshold
- The fact that we do not see an effect does not mean that there is no effect
- Currently, it is not really possible to identify thresholds

Referring to Hazard Characterisation:

If it is assumed that there is a threshold for mutagenic effects, which experimental data would then be required for identification of such a threshold?

- Different MoA should be investigated
- Most sensitive species, organs and tissues should be identified, at different developmental stages (due to, e.g., different DNA repair capacities)
- Should there be a minimum set of different cell lines/types?
- Statistical power would need to be increased, i.e. more animals per group

Referring to Hazard Characterisation:

Could it be possible to identify a NOEL, NOAEL, LOEL, LOAEL and, if so, would that be appropriate?

- If a threshold could be identified, then it should be possible to identify a NOAEL
- However, BMD calculation would in any case be more appropriate (provided that there is a dose-response relationship), irrespective if a threshold could be identified or not

Referring to Hazard Characterisation:

Which possibilities and which limitations do exist in the interpretation of studies in relation to hazard characterization for genotoxic carcinogens?

1) for qualitative approaches

- A limitation is that there is no validated test for local effects on CA
- Qualitative approaches do not provide tools for prioritization of risk management measures
- Studies on transcriptome, metabolom may contribute to improve the knowledge on MoA and interindividual variability

Referring to Hazard Characterisation:

Which possibilities and which limitations do exist in the interpretation of studies in relation to hazard characterization for genotoxic carcinogens?

2) for quantitative approaches

- Currently, we only quantify the risk based on carcinogenicity data
- Evaluation of potency may be useful, e.g. for read-across
- However, variability is a limitation, therefore, standardization of methods would be required
- normalization of results against response of positive control substances
- Epidemiological and human biomonitoring data could be useful
- Concordance between genotoxicity and cancer data can be investigated
- Quantitative approaches would allow better interpretation of risk measures (unit risk)

Referring to Hazard Characterisation:

Which tools for quantitative genotoxicity characterisation do exist and which endpoints should be addressed?

- BMD calculations would generally be possible for the OECD guideline genotoxicity studies
- Further training on BMD modelling required
- Quantitative variability of *in vivo* Comet assay data is quite high, therefore, BMDL for Comet data would be challenging
- Different endpoints and different tests per endpoint would need to be investigated

Referring to Hazard Characterisation:

Which studies could/should be used to determine a reference point?

- A test battery is needed
- The most sensitive and relevant endpoints should be covered
- (1) *in vitro* + PBPK for extrapolation to *in vivo* **or** (2) *in vivo* studies
- Human biomonitoring and epidemiological data might be helpful but there are more uncertainties than in animal studies (due to the fact that human control groups are difficult to define)

Referring to Hazard Characterisation:

Are there any AOP-related results that could be used for quantitative dose-response analyses?

- AOPs are already used for evaluation of pharmaceuticals (genotoxic and non-genotoxic substances) for weight of evidence in hazard identification and read-across
- Due to complex pathways and many tumor types, it is difficult to get data and to interpret them. At the present time, probably the carcinogenicity study is still required.
- AOP establishment is currently not relevant for quantitative evaluation
- Work on AOPs is ongoing, e.g. at OECD level

Referring to Hazard Characterisation:

Are the EFSA recommendations for BMD-modelling applicable and appropriate for BMD-modelling of genotoxicity data?

- Might be applicable for genotoxicity data
- To be checked by experts in statistics:
  - Is the statistical power of the current study designs sufficient?
  - What is a proper study design for BMD modelling?
- It was also discussed if certain aspects could have an impact on the outcome of BMD modelling (e.g. repair)

Referring to Hazard Characterisation:

Critical effect size / BM-response for mutagenic effects?

- Difficult to establish
- The critical effect size is normally considered as adverse
- Scientific reasoning for considering an effect as adverse (or non-adverse) would be needed
- Statistical power and biological relevance would need to be considered

Referring to Risk Characterisation:

Are the currently applied approaches for risk assessment of genotoxic carcinogens (MOE, DMEL) sufficient?

- May be sufficient for (most) regulated substances
- Should be improved for non-regulated substances
- There is currently no agreement on a tolerable risk (risk management!)
- It would be helpful to know more about the dose-response at low doses
- T25 does not take into account the uncertainty (whereas BMDL does)
- Mixture effects (additive / synergistic)
- The current approaches are not sufficient for genotoxic non-carcinogens
  - This could justify to apply a quantitative genotoxicity assessment

Referring to Risk Characterisation:

Pros and cons of different approaches for risk characterisation?

MOE

- Pros: it provides information on the level of concern
- Cons: is not intended to describe a risk, difficult to be interpreted by risk managers

DMEL

- Pros: it describes a risk (1/100,000 for workers and 1/1,000,000 for consumers) and leads to a permissible concentration
- Cons: More guidance from risk management on an acceptable risk would be needed

- Harmonisation of data requirements for hazard identification would be useful.
- Harmonisation of MOE and DMEL was not seen as so important

Referring to Risk Characterisation:

Does a MOE > 10,000 (calculated based on carcinogenicity data) always appropriately cover genotoxicity?

- Generally, no indications were identified which would justify to deviate from 10,000
- However, deviation from 10,000 may be possible in case of substance-specific data
- A factor for extrapolation from short-term to long-term study duration may be needed for genotoxicity data
- A systematic comparison of BMDL from carcinogenicity data with BMDL from genotoxicity data should be performed

Referring to Risk Characterisation:

Linear extrapolation from point of departure?

- More data at low doses are needed
- In the absence of robust data in the low dose range, a linear dose-response would be the default

Overall:

- Our common aim is to protect humans.
- With new knowledge, we could adopt new assessment procedures and the assessments might change