Federal Institute
for Drugs
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Risk Assessment of Genotoxic Compounds
Challenges and Future Perspectives

Risk Assessment of Genotoxic Compounds BfArM´s View

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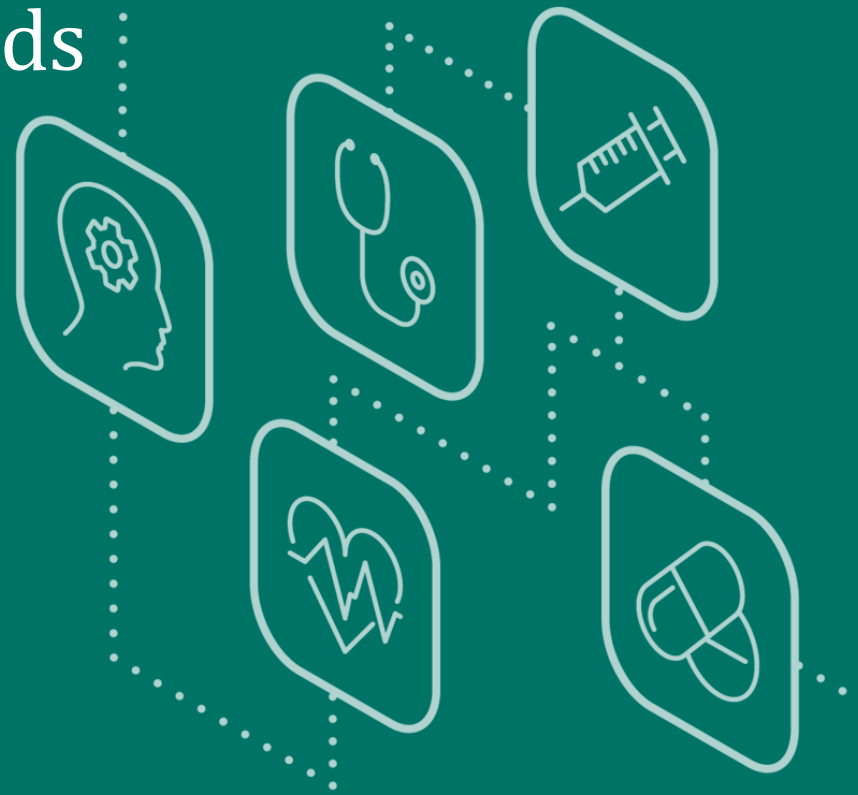

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Qverview

1. Current Approach for pharmaceuticals
2. Challenges with the current approach
3. Potential advantages of quantitative genotoxicity and current challenges for use in risk assessment
4. Requirement to overcome current limitations
5. Conclusions

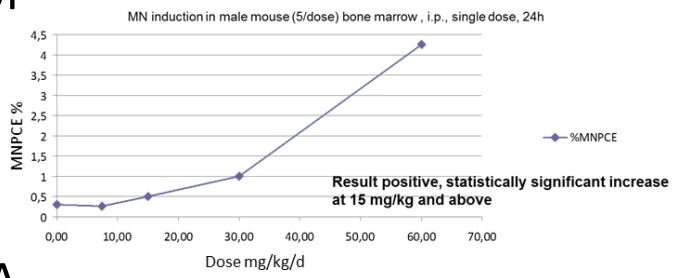
Current approach for pharmaceuticals

Current risk assessment approach for genotoxicity of active pharmaceutical ingredients (APIs) ICH S2(R1), S9

- A genotoxic potential of an API may be acceptable based on risk assessment if
  - Genotoxicity is caused by and **indirect mechanisms of genotoxicity** and it is **possible to establish a safe level (threshold)** for classes of drugs with evidence for such mechanisms
  - Genotoxicity is part of pharmacological activity of the API but **safe levels (thresholds) of exposure for human cells can be derived** for such classes of drugs (e.g. fluoroquinolones, NRTIs)

Example

Topoisomerase inhibitor tested in vivo



  - Genotoxicity is the main principle of pharmacological activity of the API. RA is based on benefit/risk evaluation. **Therapeutic benefit must outweigh the risk** (e.g. cytotoxic anticancer drugs)

Current approach for impurities in pharmaceuticals – ICH M7(R2)

- **Genotoxicants that are not DNA-reactive (non-mutagenic) typically have threshold mechanisms**
  Derivation of Permissible Daily Exposure (PDE) using No-Observed Genotoxic Effect Level (NOGEL) according to ICH Q3C (R9)

- **Focus is on DNA-reactive substances directly causing DNA damage**
  - ***DNA-reactive compounds, who are e.g. rapid detoxified before coming into contact with DNA, or induced damage is effectively repaired, may have practical thresholds***
  - ***Setting limits based on weight of evidence approach including sufficient in vivo mutation data may be possible on case by case. In vivo mutation data alone currently not sufficient.***

- **In general DNA reactive (mutagenic) substances are regulated by applying acceptable intakes (AI) calculated by linear back extrapolation of a dose with a theoretical cancer risk of 1:100,000 based on rodent carcinogenicity data**

Challenges with the current approach

Challenges for risk assessment with the current approach

- **carcinogenicity data are required** to regulate DNA-reactive mutagens above the threshold of toxicological concern (TTC)
  - generic TTC of 1.5 µg/d or chemical class specific TTC
- Conduct of **new carcinogenicity studies for contaminants not possible** (e.g. impurities in pharmaceuticals)
- **DNA-reactive mutagens are frequently identified in APIs and finished products**
- **Often challenging or even impossible** to **limit such impurities below TTC**
  (e.g. cohort of concern compounds with class specific TTCs in the ng/day range)
- **over-conservative limits** for impurities which may only have a low mutagenic potential
- **further development** of new investigational APIs may be prevented

Potential advantages and challenges

Potential advantages of the use of quantitative genotoxicity for risk assessment and challenges that need to be solved prior to the use of quantitative genotoxicity for mutagenic compounds

Potential benefits of validated quantitative genotoxcicity data analysis in approaches for risk assessment

- Less dependence on carcinogenicity datasets
- In cases were it is possible to conduct in vivo gene mutation studies to provide sufficient data for quantitative analysis and RA of mutagens health protective limits can be defined for mutagenic compounds
- Increases the data basis for and inform the development of more sophisticated IVIVE models
- Inform developments for improved (Q)SAR/In silico models for identifying and quantifying mutagenic potential of mutagens
- Inform models to quantitatively correlate mutagenic potential with carcinogenic potential of mutagens
- May lead to models to predict carcinogenic risk level of mutagens using quantitative genotoxicity data

Challenges for using quantitative genotoxicity data for DNA-reactive compounds to set acceptable exposure limits

- Currently acceptable exposure limits are calculated based on theoretical cancer risk
- It is known that increase in mutation increases risk of cancer, however any quantitative mathematical relationship is not yet validated.
- Calculating a theoretical numerical increase in cancer risk e.g. 1:100,000 is currently not possible using genetic toxicity (mutation) data.

Requirement to overcome current limitations

Research needs to foster use of quantitative genotoxicity for risk assessment of DNA reactive compounds

In vivo data

- Evaluate correlation of in vivo mutagenicity data with carcinogenicity data of compounds
- Develop and validate methods for establishing an AI or PDE based on in vivo mutagenicity data
  - define most reliable and sensitive method to measure endpoint mutation (e.g. TGR, ecNGS, other)
  - define PoD to be used
  - define uncertainty factors to be included in calculation of limit
- Agree internationally upon methodology to calculate AI or PDE from in vivo mutagenicity assay(s)

In vitro/in silico data

- Challenges for quantitative interpretation of data for risk assessment considered much greater – development of reliable and validated quantitative IVIVE approaches is considered necessary

Conclusions

Conclusions

- Quantitative genetic toxicity data evaluation is currently used in genetic toxicity risk assessment of pharmaceuticals for not DNA-reactive compounds
- Use of quantitative genetic toxicity data evaluation for risk assessment of mutagenic compounds currently not sufficiently validated for deriving acceptable exposure limits
- Validation of quantitative interpretation of genotoxicity data and quantitative correlation to cancer risk is needed for application in risk assessment of mutagenic compounds

Thank you very much for your attention!

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