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Regulatory considerations related to mutagenic impurities in pharmaceuticals

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Genetic Toxicology data are only used for quantitative risk assessment of genotoxic compounds with an indirect (not-DNA-reactive) mechanism of action. For such compounds a threshold can be determined below which no genotoxic effect is expected. Directly-DNA-reactive compounds are considered potentially mutagenic at any dose. Theoretically, even one molecule may reach and react with DNA and cause a mutation. Therefore, standard battery genetic toxicology data are primarily used to qualitatively characterize a molecule as mutagenic or not. For mutagenic molecules further assessment concentrates on the mode of action of genotoxicity to identify DNA-reactive molecules considered of high concern for human health and exempted from using quantitative genetic toxicity data in risk assessment. Such molecules are then generally regulated according to ICH M7(R1) deriving a substance specific AI based on carcinogenicity data or applying a generic TTC of 1.5 µg/d in case of lack of adequate carcinogenicity data.

Research of recent years challenges this paradigm promoting the future use of quantitative evaluation of (especially) in vivo genetic toxicology data for risk assessment of all mutagens. Few examples for using quantitative assessment of mutations to derive exposure limits of compounds have been published, e.g. EMS, benzo(a)pyrene or NDMA, using extensive in vivo mutation and mechanistic datasets. Examples with corresponding cancer data to quantitatively correlate risk for mutations and risk for cancer as the major apical disease are exceptions and have limitations. Still fundamental questions of the quantitative relationship of mutations and cancer need to be answered. A harmonized framework for evaluating the quantitative correlation of mutation risk and cancer risk is needed to use quantitative mutation data for defining health protective exposure levels for humans. A database of reference compounds to validate the quantitative relationship of mutation and cancer is recommended to support the use of quantitative genetic toxicity data for risk assessment. Definition of modifying factors needed for extrapolation of mutational risk from animal to human is considered crucial to protect humans from mutations and genetically determined health risks. For this, understanding of the crucial molecular and cellular parameters and their variability in humans is needed.

Keywords:
mutation; cancer; risk assessment; quantitative.