Session 3: Prevention Part I

Cohort of concern compounds – current guidance on impurities (especially genotoxic/ carcinogenic impurities)

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EMA Sartans with N-nitrosamine impurities
Lessons Learnt Exercise - Interested Parties Meeting
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Topics

ICH M7 principles

- **Hazard assessment and risk characterization**
- **Threshold and exposure duration considerations**
- **What is the «Cohort of Concern»**
- **Determination of acceptable limits for N-nitrosamine**

Hazard assessment and risk characterization

ICH M7 guides determination of safe limits for mutagenic compounds

Hazard assessment

- **Literature searches for carcinogenicity and bacterial mutagenicity data**
  - Classification (Class 1, 2, or 5)
- **If no data available, perform assessment of Structure-Activity Relationships (SAR) predicting bacterial mutagenicity**
  - Classification into Class 3, 4, or 5

Table 1: Impurities Classification With Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section VII (7) and VIII (8))
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive,* no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

Guideline ICH M7

ICH M7 guides determination of safe limits for mutagenic compounds

- **Safety scope:** assessment of **DNA-reactive (mutagenic)** impurities that potentially cause cancer
- Principle of Threshold of Toxicological Concern (TTC)
- Compound-specific limit
- Principle of stageing
- Consideration of benchmark dose ($BMDL_{10}$) level as an alternative to TD_{50} linear extrapolation

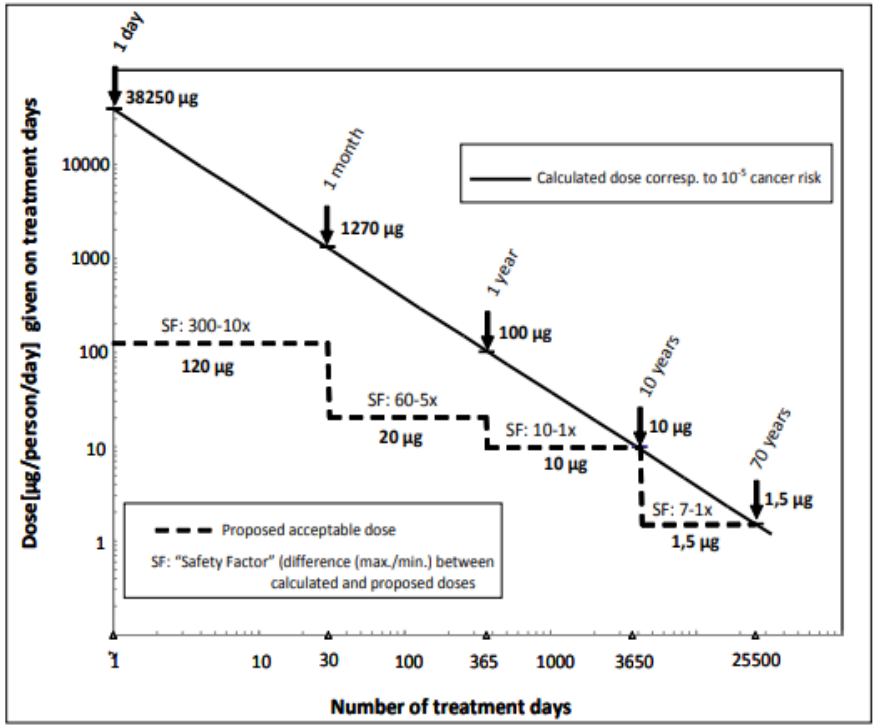


Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels as recommended in Section VII.C (7.3).

Guideline ICH M7 exposure considerations

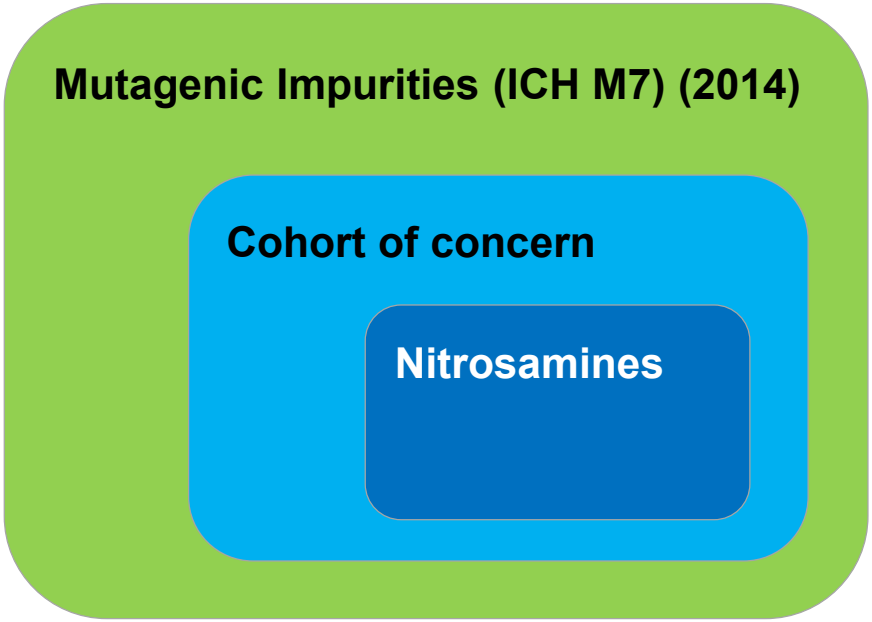
Principles of guideline appropriate to define limits for «Cohort of Concern» compounds

- ICH M7 less-than-lifetime limit (LTL) principle for shorter treatment duration
  - General:
    - Increased cancer risk of continuous low dose over lifetime would be equivalent to risk from cumulative exposure averaged over a shorter duration
  - N-Nitrosamines:
    - LTL principle also applicable to N-nitrosamines
    - Higher limits can be accepted for intermittent dosing

What is the «Cohort of Concern»?

ICH M7 principles enable determination of safe limits for COC compounds

- The «Cohort of Concern» consists of highly potent mutagenic compounds for which the generic limit of 1.5 µg/day/lifetime does not apply
- Limits can be calculated for N-nitrosamines
  - Calculation based on animal carcinogenicity data (No Observed Adverse Effect Level or Benchmark Dose Level)
- Consideration of DNA repair capacity



«Cohort of Concern» mutagens

ICHM7 principles enable determination of safe limits for COC compounds

- TD50 – dose level showing 50% tumor incidence in animal study
- Accepted life-time cancer risk level: 1 in 100’000 patients
- Dividing TD50 by 50’000
- Calculated acceptable NDMA life-time limit
  - TD50 of 0.0959 mg/kg / 50’000 = 0.000001918 mg/kg
  - To derive a total human daily dose:
    0.000001918 mg/kg x 50 kg = 0.0000959 mg/day (**= 96 ng/day**)

Summary

- **ICH M7 provides guidance for risk characterization**
- **Acceptable limits for exposure to mutagenic compounds can be determined**
  - Based on maximum daily dose, exposure duration, indication
- **Limits are based on experimental data (in vitro and/or animal data)**
  - Generic limit
  - Compound-specific limits
- **Limits can be determined for N-nitrosamines belonging to the «Cohort of Concern»**

- **Back-up**

Guideline ICHM7 – Safe Limits for Genotoxic Impurities

Principles of guideline appropriate to define limits for «Cohort of Concern» compounds

- ICH M7 provides guidance to define general and compound-specific safe limits
  - General:
    - Threshold of toxicological concern (TTC): 1.5 µg/day lifetime exposure
    - Compound-specific (class 1): Limits based on animal carcinogenicity data extrapolating to 1 : 100'000 cancer risk
  - N-Nitrosamines:
    - Cohort of Concern impurities exempted from TTC-limit
    - Toxicological principle to derive compound specific limits for class 1 compounds is also applicable to nitrosamines
      - 96 ng for NDMA, 26.5 ng for NDEA as acceptable limits (rather than fixed analytical limits)
      - Other nitrosaminnes should be limited based on the available carcinogenicity data (rather than defaulting to NDMA/NDEA limits)

Guideline ICHM7 – Safe Limits for Genotoxic Impurities

Principles of guideline appropriate to define limits for «Cohort of Concern» compounds

- ICH M7 provides guidance to identify mutagenic and carcinogenic impurities
  - <u>General:</u>
    - QSAR methods (knowledge based and statisitcal) and expert review are recommended to identify mutagenic impurties
    - Absence of structural mutagenicity alerts is sufficient to conlude impurity is not mutagenic
    - Negative bacterial mutagenicity (AMES) assay overrules positive prediction
  - <u>N-Nitrosamines:</u>
    - QSAR methods and principles are also applicable to identify mutagenic nitrosamines
    - Ames test performed under ICH and OECD applicable conditions using metabolic activation in is considered adequate to detect mutagenicity and hence, predict potential genotoxic carcinogenicity of N-nitrosamines