ICH M7(R2): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

2nd Addendum

Step 2 document – for comments

6 October 2021
ICH M7(R2) – Assessment And Control Of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk (Step 2)

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Outline

• Background
• 2nd Addendum Objectives and Work process
• 2nd Addendum monographs
• Conclusions
Background

The second revision of ICH M7(R2) includes the addition of a 2nd Addendum to ICH M7 complementing the first Addendum published in ICH M7(R1). The 2nd Addendum was signed off as a Step 2 document (6 Oct 2021) to be issued by the ICH Regulatory Members for public consultation.

- The 2nd Addendum was developed to provide additional monographs for 7 mutagenic impurities and derive Acceptable Intakes (AIs) for them.
  - Additionally, an update was made in the main M7 guideline text changing the HIV treatment duration from 1-10 years to > 10 years to lifetime.

- A Concept Paper (Sep 19th 2018) has been developed to guide the development of the 2nd Addendum.

- The EWG anticipates to finalize as a Step 4 document Jun / 2022.
2nd Addendum Objectives

• Selecting relevant mutagenic impurities to include in the Addendum

• Develop Als or Permissible Daily Exposures (PDEs) for selected mutagenic impurities based on published data

• Write monographs describing the data and process for deriving the substance specific Als or PDEs
Work process

- Stakeholders survey was performed for additional mutagenic impurities to include in the 2nd Addendum to ICH M7
- Seven mutagenic impurities commonly used in pharmaceutical manufacturing were selected for monograph development
- AIs or PDEs were derived based on the principles outlined in ICH M7
- Due to the growing length of the ICH M7 document the EWG decided to separate ICH M7 into a main guideline document and an addendum document interlinked on the ICH webpage
Mutagenic impurities included in the 2\textsuperscript{nd} addendum

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</table>
Acetaldehyde

- Mutagenic in Hypoxantine-Phosphoribosyl-Transferase (HPRT) assay in mammalian cells, while negative in Ames
- Route specific differences in carcinogenic response
- Oral exposure – no relevant carcinogenic response in rats
  - Highest doses males 246 mg/kg/d, females 260 mg/kg/d
- Significant human exposure
  - Endogenously formed as metabolite of carbohydrates
  - Exposure via food
  - Efficiently detoxified by aldehyde dehydrogenase
  - Threshold assumed
- Inhalation exposure – carcinogenic in rat
  - Nasal adenocarcinoma significantly increased at all doses tested
  - Effect of detoxification in nasal mucosa is unclear
  - Carcinogenic effect possibly limited to site of contact
  - Threshold mode of action is unclear for inhalation
Acetaldehyde - PDE (oral) 2 mg/day – AI (all other routes) 185 µg/day

- Oral PDE of 2 mg/day determined
  - Based on average daily intake from food (Uebelacker & Lachenmeier, 2011)

- For all other routes the AI is 185 µg/day
  - 28 month inhalation study in rat (Woutersen et al. 1986) considered the most relevant study
  - Relevant outcome: nasal adenocarcinoma
  - Tumor Dose (TD)_{50} calculated by Carcinogenicity Potency Database (CPDB) = 185 mg/kg/d
  - AI = (185 mg/kg/d / 50,000) x 50 kg = 185 µg/d
1,2 Dibromoethane – AI 2 µg/day

• Mutagenic in Ames and HPRT assay in CHO cells
• Carcinogenic in mouse and rat
  • By oral exposure – most sensitive forestomach
  • By inhalation – most sensitive lung and nasal cavity
• Most robust study for derivation of AI
  • National Toxicology Program (NTP) inhalation study in F344 rats (NTP TR-210)
  • TD$_{50}$ calculated by CPDB = 2.33 mg/kg/d – similar to TD$_{50}$ of most robust oral study in mice
  • AI = (2.33 mg/kg/d / 50,000) x 50 kg = 2.33 µg/day
  • AI rounded to 2 µg/day
  • One AI for all routes justified due to similar TD$_{50}$ values for inhalation and oral application
Epichlorohydrin – AI 3 µg/day

• Mutagenic in Ames and mammalian cells

• Carcinogenic at site of contact
  o Forestomach and oral cavity tumors for oral administration
  o Nasal tumors for inhalation
  o Injection site sarcomas for subcutaneous injection

• Most robust study for derivation of AI
  o Oral study in rat (Wester et al., 1985)
  o TD$_{50}$ calculated by CPDB = 2.55 mg/kg/d
  o AI = (2.55 mg/kg/d / 50,000) x 50 kg = 2.55 µg/day
  o AI rounded to 3 µg/day
Ethylbromide

- Ethylbromide is an alkylating agent and mutagenic in Ames as a gas

- Carcinogenic in NTP inhalation studies in mice and rats (NTP-TR 363)
  - Target organs were uterus, adrenal gland in males and liver in both sexes
  - Most sensitive endpoint was adrenal gland pheochromocytomas in male rat – significant increase at all doses compared to control
  - Lack of dose dependent increase - trend analyses negative and TD_{50} calculated by CPDB not statistically significant
  - TD_{50} values were calculated for each single dose by EWG and were statistically significant
Ethylbromide – AI 32 µg/day

• Derivation of the AI
  - NTP inhalation study (NTP-TR 363)
  - TD$_{50}$ calculated by CPDB not statistically significant
  - TD$_{50}$ therefore calculated by EWG for each single dose (see Note 2 at the end of the step 2 document for reference)
  - The EWG chose the most sensitive TD$_{50} = 32.2$ mg/kg/d for calculating of the AI
  - AI = (32.2 mg/kg/d / 50,000) x 50 kg = 32.2 µg/day
  - AI rounded to 32 µg/day
Note 2

• Note 2 demonstrates the calculation of TD<sub>50</sub> values for the ethylbromide dose levels in the NTP-TR 363 study:

\[
TD_{50 \, low \, dose} = \frac{0.693}{0.0215055234} \\
TD_{50 \, mid \, dose} = \frac{0.693}{0.0059671034} \\
TD_{50 \, high \, dose} = \frac{0.693}{0.0042161616}
\]

• The low dose provides the most conservative TD<sub>50</sub>
• TD<sub>50</sub> = 32.2 mg/kg/d
Formaldehyde

- **Formaldehyde is mutagenic in the Ames assay and in mammalian cells**

- **Carcinogenicity**
  - Formaldehyde was carcinogenic in animals by inhalation route for tumors in the nasal cavity
  - Formaldehyde was considered not to be carcinogenic in studies via the oral route
    - One out of three studies was positive for leukemia/lymphosarcoma, however inappropriate and deficient study design and analyses invalidated the use of this study

- **Carcinogenic mode of action**
  - Formaldehyde is considered to be a site of contact carcinogen acting mainly by cytolethality/regenerative cellular proliferation
  - Formation of DNA-protein crosslinks by formaldehyde is involved in cytolethality however, this may not be the primary mode of action
  - Conolly et al. (2004) described a model to calculate human cancer risk of formaldehyde inhalation using non-linear-based and linear-based mechanisms
Formaldehyde

• **Significant human exposure**
  o Endogenously formed – body turnover is up to 50 g/day
  o Component of many foods – daily oral intake range 1.5-14 mg/day

• **Regulatory limits**
  o US-EPA, WHO-IPCS, ATSDR, Health Canada, Canada limit formaldehyde via oral exposure to 0.2 mg/kg/d or 10 mg/day for a 50 kg person based on non-cancer endpoint
  o For inhalation HC recommends a limit of 100 ppb in air as a 1 hour average and WHO recommends 77 ppb in air as a 30 min average to protect humans from local irritation and sensitization effects
Formaldehyde AI (inhalation) = 8 mg/day or 215 ppb whichever is lower
All other routes PDE = 10 mg/day

• EWG considered the Conolly et al. (2004) model as the most suitable to derive an AI

• The AI is derived by calculating the cumulative daily formaldehyde dose inhaled at the formaldehyde air concentration associated with 1:100,000 cancer risk. This cumulative daily dose is 8.2 mg/day, rounded to 8.0 mg/day and represents an upper limit over a 24 hour period. AI = 8 mg/day

• However inhaling 8 mg formaldehyde with one breath e.g. with an inhalation drug taken once per day via an inhaler, is not considered appropriate.
Formaldehyde AI (inhalation) = 8 mg/day or 215 ppb whichever is lower
All other routes PDE = 10 mg/day

• To protect patients from local irritation and sensitization effects of formaldehyde the EWG calculated a concentration limit for inhalation of formaldehyde with drug products

• The concentration limit was derived by calculating the formaldehyde concentration in air when inhaling 8 mg over a 24h breathing period.

• With an average human breathing volume of 28.8 m³/day and weight of air of 1293 g/m³ the concentration is calculated:
  215 ppb = (0.008g/d / 28.8 m³/d) x 1/1293 g/m³)
Formaldehyde AI (inhalation) = 8 mg/day or 215 ppb whichever is lower
All other routes PDE = 10 mg/day

• For all other routes a PDE of 10 mg/day is recommended
  o Based on the limit set by US-EPA, WHO-IPCS, Health Canada, Canada and ATSDR
  o Considered broadly accepted and justified by environmental exposure ranges
  o Carcinogenicity of formaldehyde is considered specific to the inhalation route
Styrene – AI 154 µg/day

- **Styrene is mutagenic in the Ames assay only with metabolic activation and mutagenic in vivo**
  o Metabolite styrene 7,8-oxide is considered the mutagenic compound
  o Styrene 7,8-oxide forms covalent adducts with DNA, adducts identified in vitro, in vivo and, in exposed humans

- **Carcinogenic potential**
  o Styrene is carcinogenic in mice via oral and inhalation routes
  o Styrene is carcinogenic in rats only in a single study via inhalation (relevance questionable due to study limitations) but negative in another inhalation study and all oral studies
  o Styrene 7,8-oxide is carcinogenic in mice by oral and dermal application and in rat via oral and transplacental exposure
Styrene – Al 154 µg/day

• Carcinogenic mode of action
  o Metabolite styrene 7,8-oxide considered the main mutagenic agent
  o Styrene induces oxidative stress, immunosuppression and chronic inflammation are the potential contributing factors

• Derivation of the AI
  o Mouse lung tumors are considered the most relevant tumors
  o The most sensitive and robust study (Cruzan et al. 2001) provides a TD$_{50}$ calculated by CPDB of 154 mg/kg/d
  o Al = (154 mg/kg/d / 50,000) x 50 kg = 154 µg/day
Vinyl Acetate

• Genotoxic potential
  o Vinyl acetate is not mutagenic in Ames, but genotoxic causing chromosomal damage
  o Extensive evidence that genotoxicity is mediated via its metabolite, acetaldehyde

• Carcinogenicity
  o Four studies are listed in CPDB
    - Two mouse studies, one with oral one with inhalation
    - Two rat studies, one with oral one with inhalation
    - Effects were uterine, esophageal and forestomach tumors in mouse and liver, thyroid, uterine and nasal tumors in rat
  o In other published oral studies in mice and rat oral cavity, esophagus and forestomach and oral cavity and lips in rats were targets
  o Vinyl acetate was negative in an inhalation study in mice, and positive for nasal tumors in rats at the high dose
Vinyl Acetate PDE (oral) 2mg/day – AI 758 µg/day for all other routes

- PDE (oral) – vinyl acetate undergoes rapid hydrolysis to form acetic acid and acetaldehyde. Based on the same consideration as for acetaldehyde the PDE for oral route is set to 2 mg/day

- AI (all other routes): The 2 year inhalation study in rats listed in CPDB (Bogdanffy et al. 1994) was considered the most robust and appropriate for derivation of an AI. TD₅₀ calculated by CPDB was 758 mg/kg/d. AI = (758 mg/kg/d / 50,000) x 50 kg = 758 µg/day
**Mutagenic impurities and AIs and/or PDEs included in the 2<sup>nd</sup> addendum**

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Conclusions

• ICH M7(R2) restructures the format of the guideline by dividing it into two linked documents
  o First document is the main guideline including a table of all compounds, including the seven new mutagenic impurities with monographs hyperlinked to the second document
  o Second document is the addendum containing all monographs of mutagenic impurities assessed by the EWG

• HIV treatment duration changed from 1-10 years to > 10 years to lifetime in main M7 guideline text

• Seven new monographs for mutagenic impurities added plus one Note (Note 2) to explain derivation of AI for ethyl bromide

• Table with monographed mutagenic impurities edited to include new monographs

• Grammatical editing and formatting e.g. updating URLs
List of abbreviations

- **AI** – Acceptable Intake
- **ATSDR** - Agency for Toxic Substances and Disease Control
- **CPDB** – Carcinogenicity Potency Database
- **HPRT** – Hypoxanthine-Guanine-Phosphoribosyltransferase
- **NTP-TR** – National Toxicology Program-Technical Report
- **PDE** – Permitted Daily Exposure
- **TD_{50}** – Tumor Dose 50 (dose with 50 % tumor bearing animals)
- **US-EPA** – United States Environmental Protection Agency
- **WHO-IPCS** – World Health Organisation-International Program on Chemical Safety
Contact

• For any questions please contact the ICH Secretariat:

admin@ich.org